THE INTERNAL SECRETIONS

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TORONTO

THE INTERNAL SECRETIONS

For the Use of Students and Physicians

BY

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Authorized Translation of the Third German Edition

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DIRECTOR BROOKLYN DIAGNOSTIC INSTITUTE

New York

THE MACMILLAN COMPANY

1924

Set up and electrotyped.
Published June, 1924.

PRINTED IN THE UNITED STATES OF AMERICA.

TRANSLATOR'S PREFACE

The many recent books on Endocrinology are witnesses to the great importance of this subject for medical men and other working biologists. Not only is every original contributor to our knowledge of the internal secretions ardently welcomed, but each fresh method of presentation of the facts already known arouses widespread interest; and if its subject matter be well treated, every new book on endocrinology is certain of a faithful reading.

The method of presentation selected by the author of this book is so far a unique one; instead of making each separate endocrine gland a subject of information, he has chosen to elect as subjects all the important physiological functions and to describe the way in which each function is controlled by the endocrine glands, operating both separately and coördinately.

This order of treatment, has, I believe, resulted in a very valuable contribution to medical science; and I anticipate that its English version will receive a no less enthusiastic welcome than has already been accorded the book in other languages. It will be useful to all those busy clinicians who recognize how urgently every physician needs to be oriented in this subject with its many-sided applications is both diagnosis and treatment. It will be useful to undergraduates in medicine

who are striving to acquire a fundamental knowledge of the known facts in endocrinology without the aid of any comprehensive elementary treatment of the subject such as they are accustomed to in the treatment of other subjects; this much-needed comprehensive elementary treatment has been carried out in the present book and it is, in consequence, well suited to beginners, notwithstanding the fact that it contains within a small compass an immense amount of information. This latter circumstance will serve to recommend the book to many clinicians who, while not beginners in the study of endocrinology, have, nevertheless, not at all times in mind the facts that have a bearing upon their immediate problems. Specialists in other subjects may thus often find the book useful; the cardiologist will find within the limits of a single chapter all the known facts about the relations between the circulation and the internal secretions; the psychiatrist will find described here the influence of the internal secretions on the psychical life and its development; the bone specialist may learn the part that these glands play in the formation and maintenance of the skeleton; finally the connoisseur in endocrinology will be interested in examining this book from the standpoint of a critic.

One drawback attendant on the publication of most books on scientific matters it has been possible to avoid. I refer to the known circumstance that upon a subject concerning which knowledge is being rapidly accumulated it is nearly impossible to publish a book which is not considerably belated as to some of its information.

In the present book that has fortunately been avoided. The author, himself an investigator of the internal secretions, brought the third German edition up to date at the time of its publication last year; and his presence in this country has enabled the translator to incorporate in the English text additions to knowledge made since then.

To Dr. Arthur Weil, author of this book, my best thanks are due not only for suggesting additions to the text but for much valuable help in setting up the book.

J. GUTMAN.

Brooklyn, June, 1924.

PREFACE TO THE THIRD EDITION

The scepticism with which many medical men formerly held off from the study of the internal secretions has been gradually replaced by the opposite tendency which, in many students of endocrinology, is exhibited as an endeavor to interpret every change in the living human organism as a disturbance of the endocrine balance. Such one-sidedness is a great danger to every new science; it gives its opponents an excuse for attacking the very foundation upon which the science rests. As a warning against such exaggeration, I pointed out in the concluding chapter of the first edition, that it is only by taking account of the other regulating systems of the human body, namely, the central and vegetative nervous systems, and by considering the manifold influences of the surrounding world on the organism, that the physiology of the internal secretions can be investigated, and the knowledge obtained which should furnish a valid explanation of the countless, ever-changing conditions of life. In this, the third edition, I have endeavored to emphasize these relationships. Certain additions in which new discoveries are considered have also been made to the text.

To Drs. G. Guijarra (Spain), N. Ischlonski (Russia), J. Gutman (United States) and Konishi (Japan), I wish

to express my indebtedness for the interest they have shown in this book by translating it into their own languages.

ARTHUR WEIL.

New York, January, 1923.

PREFACE TO THE SECOND EDITION

That my method of treating internal secretions from the physiologist's standpoint has met with approval and success seems evident from the fact that scarcely a year had passed before it was necessary to begin revisions for a second edition of this work; and also from the fact that during this short period translations into Russian and Spanish have already appeared. I have, therefore, made no radical changes in the general structure of the book, but have limited myself to the sifting of evidence, and the insertion of new findings when these had been verified by several investigators. I have sought by additions, substitutions and new illustrations to elucidate the theoretical considerations.

I wish to thank the publishing house of Herr Julius Springer for the many courtesies extended to me and for the excellent manner in which the book was produced.

ARTHUR WEIL.

Berlin, February, 1922.

PREFACE TO THE FIRST EDITION

In the past the subject of internal secretion has generally been treated by considering the individual glands in the order of sequence in which progress was made in their study and investigation. Manifestations due to the removal of a gland and the phenomena of readjustment effected by its reimplantation, by feeding with the whole gland, or by injection of its extracts were carefully studied; disease syndromes attributed to assumed hyper-, hypo-, and dysfunctioning of glands were likewise described; also atypical constitutional manifestations resulting from congenital abnormalities of glandular development were scrupulously recorded. From the facts collected in this manner, as well as from the pharmacologic action of certain glandular preparations, information concerning the physiological functions of the endocrine glands was obtained, and hypotheses were advanced which would harmonize as far as possible with all these findings. In this way it was hoped to elucidate the relationship existing between separate living processes.

However, this mode of presentation makes it very difficult for the student of endocrinology to obtain a unified picture that will clearly show the meaning of the internal secretions in the life cycle. The information concerning these endocrine secretions is scattered, and

to learn the rôle played by the various glands with reference to a particular function, such as circulation, respiration, form-building, etc., necessitates the seeking, collecting and coördinating of data from many literary sources, comprising not only records of single investigations but of extended monographs.

This method puts the young student of endocrinology in danger of over-estimating the significance of the various glands in specific syndromes; he is likely, in making a clinical diagnosis, to be too much inclined to specialize, and to forget that the human organism must be considered as one unit, possessing an intimate connection between individual cell groups; and that a change in one species of cells produces changes in all others.

To avoid these objections, I have endeavored to present the subject of the endocrine glands from a different point of view. I have dealt with the incretions as agents concerned in the production and regulation of the separate bodily functions, and have described the part which the various incretions take in each particular life process. In this little volume, it was not possible to deal exhaustively with the entire subject of endocrinology; the book was designed only as a short survey of the physiology of the internal secretions; as an introduction to the subject for physicians and students who wish to familiarize themselves with facts that will help them to interpret for themselves the meaning of the changes in internal secretory glands which they see in particular diseases.

For a more exhaustive study of the subject I may refer to the voluminous text book of Biedl; to "The Diseases of the Endocrines," by **Falta**; to the monographs

on the male and female glands by Tandler and Grosz, Aschner, Lipschütz, Harms, and others; to the work of Oswald on the thyroid; and, finally, to the "Text Book of Organo-Therapy," by Wagner von Jauregg and Bayer.

I have refrained from giving references to literature. It would be practically impossible to enumerate without omission all the publications on the subject, continually increasing in number as they are. In his third edition, published in 1916, Biedl quotes about 11,000 references; hence, even an approximately complete bibliography would more than treble the size of the present volume.

ARTHUR WEIL.

Halle, November, 1920.

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CHAPTER I

THE ORIGIN OF THE IDEA OF "INTERNAL SECRETION" AND ITS DEFINITION

The great progress of knowledge relating to the subject of internal secretion that has taken place during the last few decades was possible only because modern medicine had achieved a scientific status, and because the fact was recognized that the same natural laws which physics, chemistry and the other exact sciences have demonstrated operating in the non-living world as likewise control all the processes of the living world.

The science of endocrinology has developed from two sources which are in their very nature diametrically opposed to each other. One source, which is analytical, comprises the highly advanced subject of biological chemistry—with its task of discovering the building stones of living substances, and of tracing the course and fate of food stuffs from their ingestion through their passage into the body cells and their conversion into the final products of excretion; and the subject of histology which is engaged in penetrating farther and farther into the minute structure of living tissues. The second source which is synthetical has a goal which is the opposite of the aims of histology and biological chemistry; its purpose is to conceive the human body as a unified organism,

to exhibit the close relationship between the cells and the organs, to explain the connection which exists between form and function—endeavors which find expression to-day in our modern conceptions of "constitution," comprising the subject of "syzygiology" (science of relation).

In 1842, in the introduction to his "Organic Chemistry in its Application to Physiology and Pathology," Liebig pointed out the fact that until the beginning of the nineteenth century the prevailing tendency in modern physiology was the analytical one, saying that, "Investigation of the purposes and functions of separate organs, and their mutual relationships in the animal body, a subject which had once constituted the principal object of physiological research, was thereby placed in the background." But these early theories of the mutual relationship of organs mentioned by Liebig had only a superficial likeness to our modern views, which strive for a unified conception of life processes. These newer views were ushered in when the cell, hitherto treated as a completely isolated object, became reinstated in its place as a component part of the whole organism.

Teachings treating of the inter-relationship of organs, described as the "concensus partium," were based upon the older view of Aristotle, as expressed in his "Correlationes," and upon the writings of Hippocrates, which Galen afterwards (130-201 A. D.) made the basis of his humoral theory. Galen believed that the blood, the splenic fluid, the bile and the mucus (phlegma) were the four juices or "humors" produced by the various organs, and that an abnormal mixture of these humors

resulted in a variety of dyscrasias and diseases. Venesection was the practical outcome of such theories, since by blood letting abnormal humors could be removed from the body. Through Bordeau (1775) the conceptions of humors were particularized even further. He ascribed to every organ the generation of a specific substance to be conveyed into the blood stream. Thus even at this early period there was already a slight resemblance to our modern endocrinology, which teaches that certain products of definite glands are conveyed into the blood and lymph streams, and that under- or overfunctioning of these glands causes an abnormal mixture of their secretions which results in disease.

The theory of *nervous correlation* originated with the progress made in histological technic and with the intensive study of the nervous system. The assumption was, that the brain was the ruler of the body; that stimuli carried by the peripheral nerves to the central nervous system kept the brain informed as to the state of the particular organs, and that this communication served to mediate the connection of the organism with the outer world. In this way the brain was thought to be able at all times to coördinate the separate activities of the distant organs into a single harmonious manifestation constituting life. This the brain was assumed to accomplish by means of stimulating and inhibiting impulses transmitted over centrifugal paths to the body organs.

With the concepts *stimulus* and *reflex* substituted for the concrete notion of humors ideas were introduced into medicine which involved the danger that they would lead

into philosophical speculation rather than to the firm ground of scientific knowledge. Efforts were made to avert this danger by advancing the hypothesis that the constant chemical changes of metabolic origin occurring in the cells acted as stimuli to the nerve endings, and that the transmission of these stimuli was an electro-physical phenomenon. These stimuli were supposed to influence the metabolism of certain ganglion-cell centers in the brain, and the resulting changes in these ganglion cells would act again as stimuli to be transmitted to the peripheral cells. Furthermore, it was soon learned that the masses of ganglion-cells in the intestines, heart and other organs are independent nerve centers which control the automatic activity of the respective organs, and which, like the glands of the body, are connected with the brain and spinal cord through the autonomic nervous system.

These views concerning the nervous regulation of all the life cycles dominated physiology until very recently. To the blood was assigned only an auxiliary task, that of a carrier whose function it was to deliver nutritious material to the individual cells, to relieve them of their waste products of metabolism and to transport these to glands and other structures concerned with the elimination of useless, excretory substances. Although, in general, the main function of the blood was thus correctly assumed, one fact was nevertheless overlooked, namely, that the blood was a genuine connecting link between the numerous organs, and that these organs might influence each other through the excretions they poured into the blood stream.

Other pictures also fitted very badly into this frame; for example, certain glands, like the thyroid, have no excretory ducts; hence, these organs were thought to be simply useless survivals from an earlier developmental period. Little attention was also paid to the manifold observations made in the clinic, and to the many illuminating physiological experiments which indicated beyond a question of doubt that the conception of all-powerful nerve centers was not justified; that many metabolic processes were carried out automatically and without any participation of the nervous system; and that the brain can be directly stimulated by products of cell metabolism circulating in the blood and lymph currents without the intervention of peripheral nerves.

In 1849 Berthold showed for the first time that after the severance of all nerve connections between the brain and the testicles the sexual impulse remained normal. Through removal of the testicles from young cocks and transplantation of these organs under the skin of some other part of the body, this investigator succeeded in retaining in the cock its masculine characteristics, whereas in those birds in which the transplantation was not made, or was unsuccessful, features were obtained that were characteristic of the castrated type, the capon. These facts caused the theory of *nervous correlation* to be discredited.

The older conception that sexual instinct and secondary sexual characteristics are dependent upon steady stimuli sent to the central nervous system from the cells of the reproductive glands and transmitted over the

peripheral nerves, and that, by a reverse process, the masculine or feminine organization of the brain determines a growth of body cells into certain specific sexual forms, was contradicted by these experiments. In spite of their importance. Berthold's observations were scarcely noticed, and they were soon completely forgotten. Forty years later, however, Brown-Sequard, who was then seventy-two years old, reported to the French Academy of Sciences his personal experiences with testicular extract. This announcement created a great uproar and aroused the interest of the whole world. He reported his remarkable rejuvenation through the use of testicular extract: increased muscular power; a subjective feeling of greater pleasure in work; improved functioning of the gastro-intestinal tract, and other regenerative symptoms similar to those that have lately been produced by Steinach in senile rats and in old men in whom the vasa deferentia were ligated. Brown-Sequard's experiments, which have since been repeated and substantiated many times, constituted a new argument against the overwhelming influences that had been ascribed to the central nervous system in the regulation of life phenomena. His experiments showed for the first time that there were in the body chemical combinations of still unknown composition which directly affected either the body cells themselves or definite nerve centers, and that the effect could be produced through the circulating blood, and did not necessarily arise as a stimulus travelling over centripetal paths to the brain. These experiments also constituted a practical confirmation of the older views of

Claude Bernard who had taught many years before that besides the secretions which the glands of the body poured out through their ducts they also made specific compounds which found their way into the circulation, and that by means of these substances transmitted into the blood stream other glands and distant organs could be influenced. He spoke of a *sécrétion interne,* and a "*sécrétion externe,*" and thus he is, indeed, the originator of our modern expression *internal secretion.*

As to the nature of these specific gland products, or as to the exact place where they were produced, there were at first only hazy conceptions; workers were satisfied to accept the interna secretions as given entities and to study their functions through observations derived from an abundant clinical material; through the manifestations produced by removal or transplantation of the glands; through gland feeding, and through injection of glandular extracts. These studies brought an ever-stronger conviction that besides the *nervous correlation* of organs there must exist other means by which these organs act upon one another—means independent of the nervous system and competent to stimulate or inhibit the activity of separate organs through the action of specific substances carried to them in blood or lymph. These substances were looked upon as messengers from cell to cell and, in accordance with the proposals of Bayliss and Starling, were named *hormones.* Later, Abderhalden, following a suggestion of Roux, introduced for them the term *incretion,* in contradistinction to the term *excretion.* Other names, such as *autocoids,* for

stimulating hormones, and *chalons*, for depressing hormones, proposed by Schafer, have not been adopted, because, as we shall see later, the same hormone may have, in accordance with its point of attack, either a stimulating or an inhibitory action upon a particular function.

The development through which this subject of research has passed may be best understood if the first definition of Brown-Sequard is taken as a starting point. He states: "We assume that every single tissue and, in general, every separate cell of the organism secretes certain products or ferments which are poured into the blood current, and which through the medium of the blood may influence every other cell. In this way a solidarity is established between all the cells of the organism by means of a mechanism other than the nervous system." In this definition the idea of an incretion is still quite general; every product of cell metabolism which enters the blood, even an end product which is later destined to leave the organism as waste, is here included in the category of the internal secretions. Urea and carbon dioxide, for instance, while on their way to the kidneys and the lungs, and still able to influence other organs, would thus come under the definition of hormones. Indeed, animal experimentation has shown that urea injected subcutaneously causes an increase in the decomposition of protein substances, and that carbon dioxide in the blood excites the activity of the respiratory center—facts which according to this definition would make them hormones.

Should we go into the study of internal secretions from this standpoint there would be no solid ground upon

which we could work; for the extreme multiplicity of intermediate and end-products of metabolism, and the countless different relationships between the numerous cell groups, would make any general apprehension of the subject impossible. Moreover, Brown-Sequard's definition assigns to each cell a twofold function, one of doing its own specific work, the other of forming a special *ferment* to serve for *humoral correlation*. It was recognized, by degrees, that the latter task is not allotted to every cell of the organism, but only to groups of cells arranged in a certain manner and forming a peculiar type of glands. In these glands the histological structure, consisting essentially of groups of secretory epithelial cells surrounding abundant blood vessels, and with no outlet in the shape of ducts, clearly indicates the direction which their output must take, *i.e.*, their secretions must pass into the blood current. These structures were, accordingly, named endocrine or blood glands, the purest type being represented by the parathyroids, the thyroid, the pineal gland, and the anterior and middle lobes of the pituitary.

Besides this pure type, another, an atypical group of glands, soon became recognized as belonging to the endocrine system. This group is represented by the pancreas and the gonads. These organs were first regarded as functioning only by means of products poured out from their ducts, but it is now known that within their parenchyma reside special types of cells that add to the blood a specific hormone. In the pancreas these cells comprise the islands of Langerhans; in the germ glands it

is the interstitial cells lying between the germinal portions which produce the internal secretion. In a third type of endocrine glands, incretion is associated with the production of morphologic elements which find their way into the blood stream. To this group belongs the thymus; the latest investigators also add the spleen to this class.

The posterior lobe of the hypophysis and the medulla of the suprarenal gland deviate from the epithelial structure characteristic of all other endocrine glands. These glands are, nevertheless, counted as members of the endocrine chain because they possess the specific chemical attributes of an endocrine gland; they produce a specific substance (pituitrin and adrenalin) which no other organ produces. All these types of endocrine glands have one common property which they owe to the peculiar characteristic of hormones, *i.e.*, they can stimulate organs far removed from themselves.

Among the endocrine glands, Gley includes the liver. This would be justifiable if the classification were made on the basis of its histological structure (epithelial cells, glandular arrangement, adjacency to blood vessels), but if the nature of the substance it contributes to the blood is taken as the basis of classification, then its inclusion among the endocrine glands is not justified, for glycogen is neither a product specific of the liver alone, nor does it possess the characteristics of other incretions; that is, it has no appreciable action if used in very minute quantities, but, on the contrary, the action of glycogen is in direct proportion to the amount of energy it contains, and, hence, does not resemble the action of a catalytic—a prop-

erty which characterizes all genuine hormones. Glycogen serves purely as nutritive material like fat.

The *panniculus adiposus,* a "non-glandular organ which plays, nevertheless, the rôle of an endocrine gland," is according to our conception also no internal secretory organ. The same is also true of the *plexus choroideus* and its secretory product the *liquor cerebrospinalis,* a secretion to which not only the ependyma of the ventricles contributes, but most probably also the pia; this fluid, originating from two different sources, is evidently not a true incretion.

Gley, in accordance with his more generalized conception, classifies the internal secretions as follows:

(1) *Internal secretions* which serve as nutritive material; (2) morphogenetic substances, *hormozones,* which play their important rôle through the control of tissue-building during the ontogenetic period; (3) *hormones* which stimulate the functional activity of organs; and (4) *parhormones* which produce detoxication through bringing about the conjugation of injurious metabolic products. This classification cannot well be followed, since the difference between hormozone and hormone cannot be strictly upheld. We shall see later, for instance, that the morphogenetic effect produced by the interstitial cell secretion of the germ glands depends precisely upon whether the secretion stimulates or inhibits organic functions thus bringing about alterations of metabolism that accelerate or retard cell division. The mucous glands of the duodenum and jejunum, though they do not fit into our classification, must nevertheless be added to the en-

docrine system, since these glands produce a specific substance, a hormone, secretin, which stimulates the secretion of pancreatic juice.

The definition of "internal secretory gland," which we shall adhere to in our subsequent treatment of an *internal secretion,* is the following: *Glands conforming to a definite histologic type, with a structure peculiar to each gland; manufacturing specific chemical combinations and delivering these to the organism through the blood and lymph channels, producing by means of infinitisimal quantities of these specific substances certain definite effects upon the functions of other body cells, without furnishing material for cell building.*

As a basis for the assumption that the chemical structure of every glandular hormone is specific, we have the chemical composition of the incretory products so far isolated; adrenalin from the suprarenal gland; the crystaline hypophysin product from the pituitary; and the newly discovered thyroxin, which is evidently a hormone of the thyroid. The question whether every endocrine gland produces only one or a number of specific products remains unanswered for the present. We meet with further difficulty when we attempt to answer the question whether the incretions are products altogether newly manufactured from the nutritive materials and the intermediate substances of cell metabolism circulating in the blood current, or whether these hormones already exist in the food and blood, and are only appropriated and distributed by the glands. The great scepticism which prevailed in regard to the synthetic powers of the organism

before Woehler accomplished the synthesis of hippuric acid from benzoic acid and glycocoll has lately been replaced by the opposite inclination, a tendency to credit the organism with immense synthetic powers, in spite of the fact that recent observations concerning protein building from aromatic amino-acids show specific bounds to the synthetic ability of the organism. In addition to this proof that there are limits to the capacity of the animal cell to manufacture its own materials, the knowledge which we possess concering the indispensable vitamines (nutramines), which cannot be manufactured by the animal organism and must be supplied by the food, should guard us against an overestimation of the synthetic powers of the body. The close resemblance existing between certain deficiency diseases (diseases due to lack of particular vitamines) and diseases of the endocrine glands —the resemblance of pellagra, for example, to Addison's disease—has recently led many investigators to question whether the vitamines may not be either precursors of particular hormones, or the hormones themselves, stored within the endocrine glands. We shall discuss this question more fully in a later chapter.

At the present moment the conception of endocrine functions to which the greatest importance is attached is that these glands dominate the life cycle by the production of certain substances which act on other organs as stimulating agents. Another hypothesis supposes that it is the function of these glands to take poisonous products of metabolism and to render these poisons harmless by binding or reconstructing them. As a model for

such hypothetical detoxication we have the known behavior of the liver, which renders the ammonia resulting from the desamidization of amino acids harmless by converting ammonia into urea; and which also transforms a great variety of other decomposition products into indifferent substances, storing them as glycocoll, urea, etc. Another such hypothetical detoxication function is attributed to the thyroid, which is thought to abstract iodine from the circulation and to combine it in the form of harmless proteo-iodine compounds—an hypothesis seemingly sustained by the presence of an iodine-containing protein discovered in the thyroid in 1895 by Baumann. But the detoxication hypothesis is not applicable to every case; the experiments of Brown-Sequard indicate that the action of the testicular juices must have been of a stimulating character, for the small quantities he used excluded the likelihood of their possessing a detoxicating function. Besides, if the endocrine glands were detoxicating agents, poisonous symptoms of some sort would appear after their removal, since, in their absence, the toxic substances, being no longer bound, would not be restrained in their activities. But we know that though certain definite changes in metabolism may be produced by the loss of certain glands as, for example, in castration, there need, nevertheless, be no immediate serious toxic effects produced by their absence.

After the removal of the thyroid, toxic substances have never been found in the blood (Bachmann and Asher). Hence, it may safely be assumed, as a general truth, that the disturbances in the normal processes of life which

appear after the removal of an endocrine gland are due to the lack of its secretion and not to a flooding of the organism with poisonous products of metabolism because of the absence of a detoxicating agent. This view has become the guiding principle in the application of endocrinological science to various disciplines of medicine; the diseases of the thyroid (Basedow's disease, myxedema, cretinism, etc.), of the hypophysis (acromegaly, dystrophia - adiposo - genitalis), of the parathyroids (tetany), or of the gonads (eunuchoidism), are, in the light of our present knowledge, ascribed to an altered secretion of the respective glands as the result of their hyper- or hypo- or dysfunctioning, and not to a lack of detoxication. Upon this view also the therapy of endocrine gland disturbances is based; a deficiency in hormone secretion must be made up, however this may be accomplished; whether by implantation of a healthy gland; or by the administration of the whole gland or its extracts; or by the injection of appropriate gland preparations. In cases of abnormal secretion the remedy may be sought in the removal of the diseased portion of the secreting gland, as is not infrequently done in Basedow's disease.

The theory of detoxication received its chief support from the rapid deterioration observed in animals after the removal of the parathyroids or the adrenals. Loewi and Gettwert found that the serum of adrenalectomized guinea pigs injected into frogs stops the heart in diastole. This action they could prevent by the use of atropine. They concluded from this that a poisonous substance, probably cholin, is present in the serum of an adrenalec-

tomized animal. We shall learn in another chapter that the base cholin is found chiefly in the cortex of the adrenals, being combined there in the form of lecithins, while the adrenal medulla contains a blood-pressure-raising substance, adrenalin, the absence of which is followed by a marked sinking of the arterial tension. Two entirely different functions seem to belong to this one endocrine gland, a detoxicating function associated with the storing up of cholin, which is capable of binding other metabolic poisonous products, and another, a genuine incretory function, which is dependent upon the action of adrenalin.

The practical applications of the science of endocrinology is much older than its theory. The recognition that the sexual glands had great influence on growth and on body form goes back at least to Biblical times, during which castration was already practised upon animals designed for food, with the object of favoring the accumulation of fat. Later, various disturbances thought to be due to disease or deficiency of certain glands were treated by feeding the sick with such glands or with other tissues of healthy animals. Thus was laid the foundation of our present *organo-therapy.* Such methods of healing disease we find mentioned as early as 1400 B.C. in the Indian Ayurveda of Susruta; they may be traced from the very earliest times through the gruesome pictures of the religious painters, and the rich treasures of dried animal and human organs of medieval apothecaries, quite down to the nineteenth century.

However, the conceptions which prevailed in regard to

the curative properties of normal tissues were of an exceedingly general character. Such tissues were regarded as carriers of secret *soul substances* which were stored primarily in the blood so that the organs richest in blood, like the liver, were considered most potent in the cure of disease. Paracelsus (1493-1541) was the first to propose the replacement of a diseased organ by a healthy one; he was, therefore, the first to recognize the specific influence which particular tissues have upon the regulation of life processes, although he was of course unable to think of biochemical reactions according to our present-day conceptions.

Attempts have repeatedly been made to classify the endocrine glands into groups. They have been classified in numerous ways according to the standpoint of the author; embryologically, histologically, physiologically. All these attempts have led to no satisfactory results, and they must continue to remain fruitless because no two glands are uniform in structure, each gland representing a mixture of different embryonal aggregates (Keimanlagen). Their functions, too, may be changed by influences exerted upon them by the joint activities of other glands, by the existing state of the body, and by the greater or lesser irritability of the individual cells of the whole nervous system. Any schematic classification seems even more difficult to make, when we remember that the individual endocrine glands might each produce several hormones capable of inducing entirely different physiological effects.

The most widely recognized classification seems to be

the one proposed by Falta. He differentiates hormones into those that increase metabolic processes (accelerating or dissimilatory-catabolic of Biedl), and those that retard metabolic processes (retarding or assimilatory-anabolic). In the first group he places the thyroid, the posterior pituitary lobe, the chromaffine system and the germinal portion of the gonads; to the second group he assigns the parathyroid, the anterior lobe of the hypophysis, the suprarenal cortex, and the interstitial germ glands. However, even this classification, as we shall see later, is not quite logical, especially as regards the gonads, since their incretion affects the metabolism of different body cells in quite different ways; also the function of adrenalin, the hormone of the suprarenal bodies, varies in correspondence with variations in the functions of the sympathetic nervous system; consequently the suprarenal function does not fit into this classification.

We shall, therefore, in our future discussions, avoid all schematization, and choose as a basis for our description the physiological functions of the internal secretion. We shall endeavor to show to what extent the individual endocrine secretions take part in the physiologic processes of the life cycle. As an introduction to this study we shall briefly consider first the embryological development and the histological structure of the different incretory glands, but only insofar as these considerations are necessary to the understanding of their functions.

CHAPTER II

EMBRYOLOGY AND HISTOLOGY OF THE ENDOCRINE GLANDS

The question has frequently been asked whether the production of incretions is the sole function of particular cell groups so that wherever incretion and excretion is carried on within a gland these functions are confined to separate morphological elements, or whether one individual cell may assume this double rôle. The conception that in the pancreas the cells of the acini have an excretory function and those of the Langerhans islands an incretory function has encountered many attempts at refutation, because in some cases of diabetes mellitus with marked disturbances in carbohydrate metabolism completely intact islets of Langerhans are sometimes to be found. But this apparent discrepancy has recently been cleared up, for very painstaking histological investigations have shown that there is in these cases an altered staining of the granules in the cells of the islets, an alteration which points to a disturbance in their function. Added to these observations is also the suggestive circumstance found by Banting and his co-workers that a pancreas of which the excretory duct had been artificially occluded for several weeks, so that the acini had degenerated and the Langerhans island cells had increased in number, furnished an extract which when injected into a

subject with diabetes mellitus was much more potent in reducing the sugar content of the blood than is the extract obtained from an ordinary gland.

In the case of the gonads, also, with their double rôle of producing an internal secretion in addition to the giving off through their ducts of elements concerned with reproduction, there is still a question whether the reproductive portion of the male germ gland, the spermatogonia and the spermatocytes, has also an incretory function, or whether the incretory function belongs exclusively to the cells of the interstitial portion. However this may be, the development of the male secondary sexual characters is independent of spermatogenesis, since even in cryptorchism (undescended testicle with degenerated germinal elements) the secondary sexual characters are well developed, and since, on the contrary, reproductive ability may coexist with a male eunuchoid type approaching the female body form.

The other endocrine glands possess only *internal* secretory cells and have no excretory tasks, but the secretory portions of these glands sometimes arise from more than one germinal layer, and these portions of different embryological origin have also different functions. In some of the lower animals the thyroid and the anterior lobe of the hypophysis remain connected with the stomodeum through their excretory ducts and retain certain excretory functions; in man, also, vestiges of the excretory ducts, the thyroglossal and hypophyseal ducts, are occasionally met with, the latter being frequently observed in acromegaly.

The Thyroid Gland (*Glandula thyreoidea*)

In the human embryo the thyroid gland originates from the pharyngeal epithelium. It arises as a ventral, mushroom-like outgrowth with a stalk which becomes constricted in the course of development and disappears through atrophy. The gland soon forms into a two-lobed organ, the lobes lying at either side of the larynx and being united by a narrow portion, the isthmus. The mass of cells, originally compact, is later invaded by strands of fibrous tissue and is subdivided into single-layered columns of cells which continue to increase numerically. Soon rounded, hollow vesicles are formed, which consist of one layer of flattened epithelium and are filled with small quantities of fluid derived from broken-down cells or their secretions; these rounded, hollow, fluid-containing chambers are 40-100 microns in diameter and form the thyroid follicles (named by Kohn thyroid vesicles). In many places these follicular new formations remain united by means of epithelial strands; at other places these connections disappear through canalization and pressure atrophy, so that, finally, the fully formed gland of the human organism becomes an aggregation of simple glandular tubules which have no connection with each other and which have not originated by branching or budding, as is usual in gland formation (Heidenhain).

The hollow interior of the follicles is filled with a fine, glassy, tenacious mass, the colloid, which when freshly excreted by the cells stains but poorly with fuchsin. It

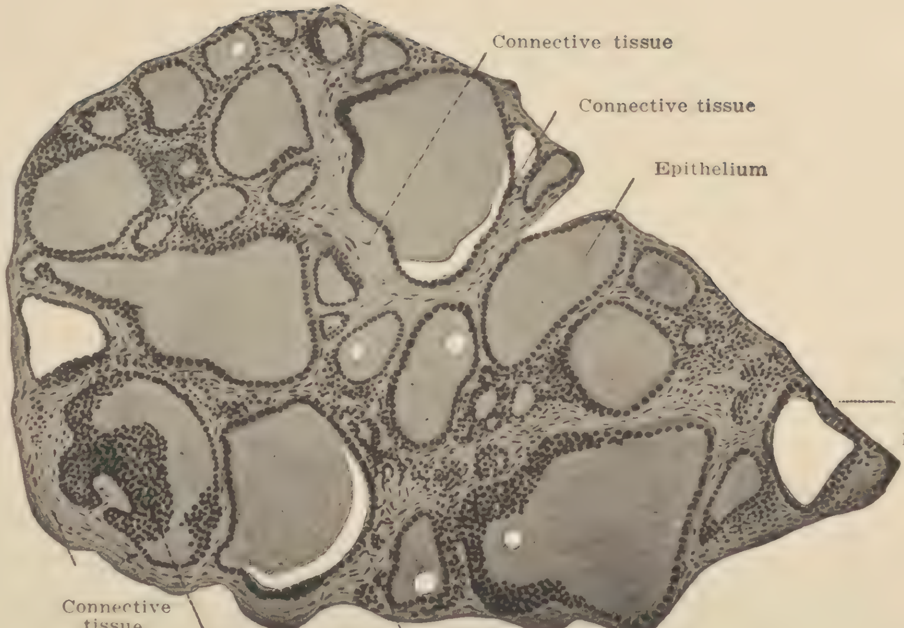


FIG. 1. Thyroid of a 37-year-old man (about × 250). (After Rauber-Kopsch.)

is only through the admixture of particles of degenerated cells that it assumes the better staining qualities which it owes to the fuchsinophile character of the added degenerated cell particles. The follicular cells, according to Krauss, also secrete, besides the colloid, another incretion, which is found within the follicles and consists of fine, tannic acid-fast granules already to be discerned within the cells proper.

It seems that in the different disturbances of the thyroid the degree of dispersion of the colloid material or the manner in which it is distributed within the gland, and not merely its absolute quantity, is subject to considerable variation. For instance, in Basedow's disease, the colloid material is more extensively scattered and is therefore more readily diffused into the lymph and blood streams, whereas in goitre it is collected in larger masses, making diffusion more difficult. Variations in the distribution of the colloid explain, perhaps, the great flooding of the blood with the specific thyroid incretion in those cases of hypersecretion which are not associated with visible enlargement of the gland.

The question has not yet been indisputably decided whether the colloid, which is accumulated and stored within the vesicles of the thyroid and is gradually released into the blood current through the intercellular spaces and broken-down cell walls, really represents the specific secretion of the thyroid, or whether the cells pour another incretion directly into the blood and lymph currents. The compact network of capillaries and lymph channels which is woven about the separate follicles pro-

vides for a rapid and intensive exchange of material between blood and parenchyma cells. The rich supply of blood vessels (superior thyroid artery from the external carotid, and inferior thyroid from the subclavian artery) procures for the organ a most generous flooding with blood; it is estimated that in one minute 560 cubic centimeters of blood traverse 100 grams of thyroid tissue, whereas to the same volume of kidney only 100 cubic centimeters of blood is supplied in the same time, and to the resting muscles only 12 cubic centimeters. Therefore, sixteen times the amount of all the blood in the body, flows through the thyroid each day.

The nerve supply of the thyroid is derived from the cervical sympathetic, which supplies its vaso-dilator fibres, and from the superior pharyngeal nerve, supplying its vaso-constrictor fibres.

In some cases the main thyroid mass is augmented by a horn-shaped addition extending from the isthmus backward to the hyoid bone; this extension persists as a remnant of the ductus thyroideus already mentioned. In addition, there are also a number of small thyroid tissue nodules, accessory thyroids, which, after removal of the main gland, may undergo hyperplasia and mitigate the symptoms of thyroid insufficiency resulting from thyroid removal. These accessory thyroids are usually situated in the fat which occupies the space between the base of the aorta and the lower margin of the mandible.

When transplanted into an animal of the same species, the thyroid gland retains its funct n; its follicle forma-

tion and its secretion continue, provided the blood supply is adequate. Heterotransplantation, also, is often successful when the generic relationship between the two animals is not too remote. Voronoff succeeded in transplanting the thyroid from a chimpanzee to a human idiot in whom the gland remained functional for fully six years.

The Parathyroid Bodies (*Glandulæ parathyreoideæ*)

These arise from the epithelial rests which are originally connected with the dorsal end of the third and fourth branchial grooves; their place of origin is, therefore, near that of the thyroid. In the human being the four parathyroids (3-15 mm. long, 2-4 mm. wide) are situated in two pairs on the posterior surface of the thyroid, and on this account they were completely overlooked by the older anatomists; as late as 1864 Virchow described them as accessory thyroids.

Contrary to those of the thyroid, the embryonic cell accumulations of the parathyroids retain their compact form and but seldom show a tendency toward vesicle formation. In man the cell groups branch out into a few broad strands, separated here and there by interpolated fine bundles of fibrous tissues, thus forming a small number of lobules. The few follicles occasionally present are filled with poorly staining colloidal material; their incretion, which in its preliminary stage consists of very fine granules that react to fat-staining dyes, is delivered directly into the minute capillaries of the in-

ferior thyroid artery, or into the numerous extremely fine lymph vessels.

In some species of animals (cats and rabbits) accessory parathyroids are found in the loose connective tissue

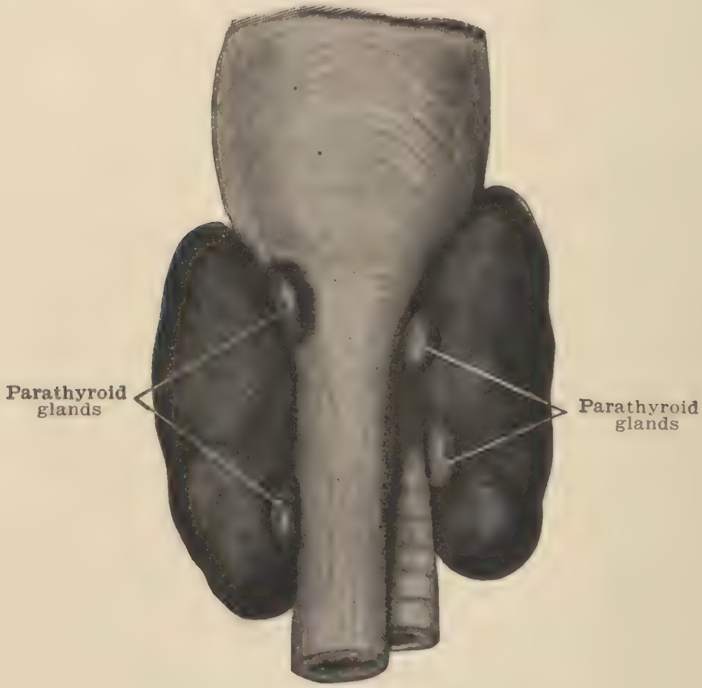


Fig. 2. Human parathyroid glands (Zuckerkandl).
Seen from the dorsal side.

accompanying the trachea; they may also be found imbedded in the thyroid gland. After homotransplantation the parathyroid graft continues active and functional for a long period, during which the symptoms that ordinarily follow parathyroid removal may remain absent.

The Pineal Body

(*Epiphysis, Corpus pineale, Conarium*)

This gland is considered here because, like the thyroid and parathyroid, it originates from a single anlage and is not, like the human endocrine glands that remain to be described, formed by the fusion of more than one anlage. It is possible to identify the pineal gland in the embryo as early as the 5th week; it is formed there as a glove-fingered evagination from the epithelial covering of the mid-brain; it rests upon the surface of the corpora quadrigemina. The fully developed organ weighs about 0.2 grams, is 8 millimeters long, and 6 millimeters wide. Histological examination shows that the primordial utricle has become converted into a compact mass of glia cells which become subdivided into separate sections by broad bands of fibrous tissue. The cells are joined to each other by very fine fibrils, but from the seventh year upwards the continual increase in the growth of the fibrous tissue forces the cells apart and separates them from each other. In the meantime, particles of calcium carbonate, calcium phosphate and magnesium phosphate, visible even to the naked eye—the so-called brain-sand—become deposited in the glandular tissue; this is apparently a sign of senile involution in the life of this gland. The original glandular cells, the pineal cells, are distributed through the glia reticulum; nerve fibres terminating in spherical end bulbs thought to be axis cylinders invade the glandular tissue (Walter's Randgeflechte),

What is considered the incretory material of this gland consists of fine acidophile granules scattered through the weakly staining protoplasm of its cells; according to Josephy and Sacrista the peculiar spherules observed in the nuclei may be the incretory substance.

The Thymus (*Glandula thymus*)

This organ represents a transition to that group of compound endocrine glands which are formed from the union of several different tissues. Like the thyroid and parathyroid, the thymus also originates from pharyngeal epithelium, namely, from the third branchial groove. From this two paired, utricular projections arise and become lobulated by grape-like outgrowing additions. In children this organ consists, when fully formed, of two long, narrow lobes, occupying the anterior medastinal space. They are situated in front of the great vessels and of the pericardium, and are frequently united to each other at their lower end. At birth the gland weighs about 15 grams, at the age of two, 25 grams, and at puberty about 40 grams. After that it begins gradually to atrophy, so that at 45 it weighs hardly 10 grams. (Compare illustration 24).

A histological study of the gland in the newborn child shows numerous strands of fibrous tissue growing from the capsule into the innermost part of the gland; these strands subdivide the lobes into many smaller lobules, each about 20 millimeters in diameter; when stained these lobules show darker cortical and lighter medullary areas that are connected by thin strands of medullary

tissue. The fundamental structure of the lobules consists of a reticulum of large epithelial cells, descendants of the original entodermal pharyngeal epthelium, cells connected with each other by fine processes extending in

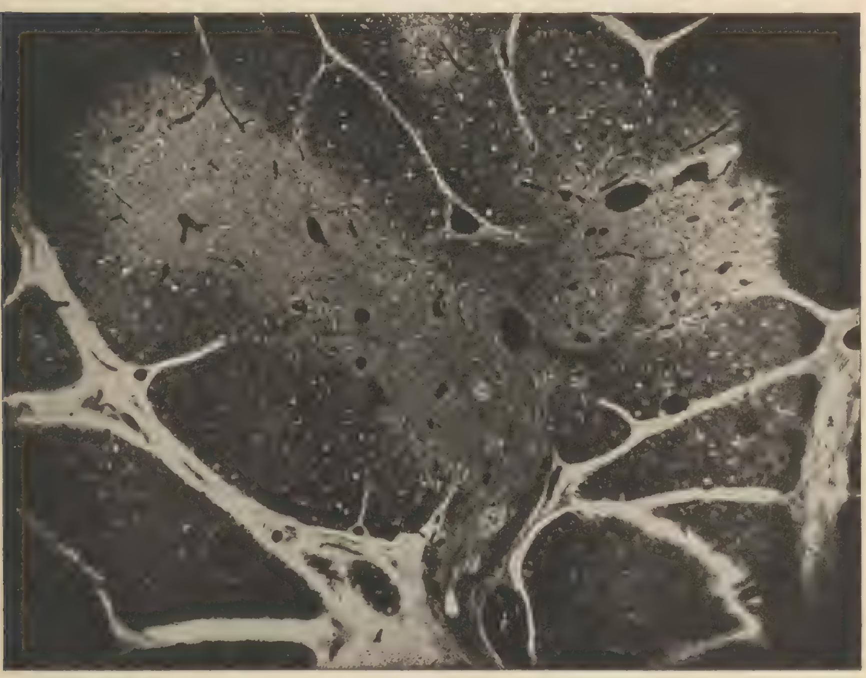


FIG. 3. Human thymus. Microphotograph.
No. 2 eyepiece; A A lens (Zeiss).

all directions. In the meshes, particularly in those of the medullary substance, there are found from the beginning of the second month smaller cells, 4 to 7 microns in diameter, which appear of darker color on the faintly staining medullary background. In the lighter medullary portion Hassall's corpuscles are located. These consist

of concentrically layered epithelial cell accumulations of mesodermal origin with keratinized central portions; they measure in all about 130 microns. These corpuscles were at one time thought by some investigators to be the active hormone-producing part of the thymus, but others looked upon them only as cell groups in process of degeneration. (Dustin.)

After puberty the cellular element becomes displaced by the constantly increasing fibrous tissue, and within the interstices of the capsule fat cells settle, so that in the aged but very few lobules of the gland are to be found; in these the small lymphocytic cells appear to have entirely disappeared and to have been replaced by the larger medullary epithelial cells.

The blood supply of the thymus is derived from the internal mammary artery, the thymus branches of which form a thick capillary network within the capsular tissue of the gland.

The Suprarenals (*Glandula suprarenalis*)

The suprarenal gland is another true internal secretory organ derived from two different anlages which are formed from different germ layers; the descendants of these two embryonic cell masses are not fused so completely as are the different constituents of the thymus. A macroscopic examination of the gland shows a yellowish cortex and a lighter, gray medulla; these, we shall call, according to Kohn, the epithelial (cortical) layer of the suprarenal and the chromaffine (medullary) portion. In the lower vertebrates, the cyclostomes, selachi-

ans and teleosts, we find these portions arranged in separate organs, the epithelial part constituting the interrenal organ or mesonephros, the chromaffine portion be-

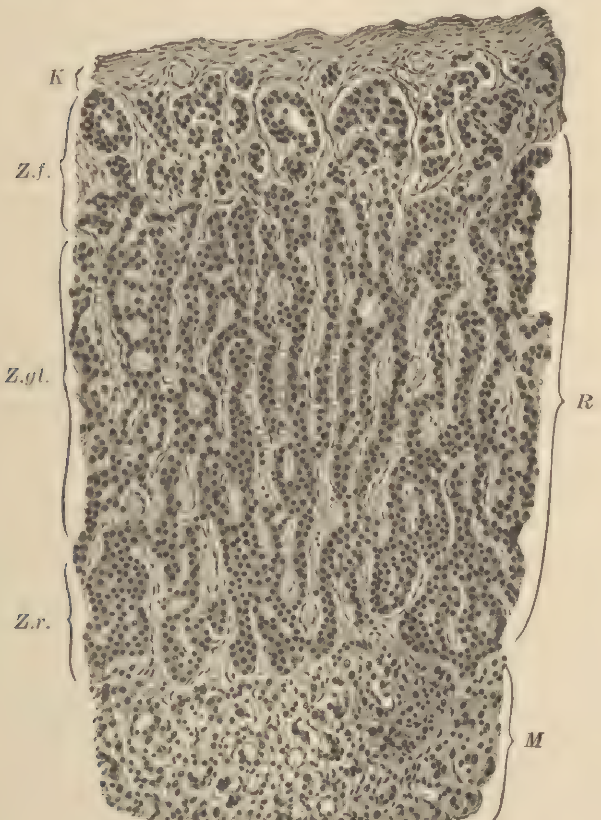


FIG. 4. Suprarenal of Man (about × 80).
K, capsule; *R*, cortex; *Z.gl.*, zona glomerulosa; *Z.f.*, zona fasciculata; *Z.r.*, zona reticularis; *M*, medulla.

ing the suprarenal body proper or phaeochrom body (so named because of the characteristic brown color of the cells when stained with chromic acid).

The outer part of the suprarenal bodies, the cortical layer, originates as a solid mass of cells in the neighborhood of the germ glands and from the same mesothelial layer of the celome. The close morphologic relationship between the germ glands and the suprarenals, shown in embryonic life by similarity of origin, is also evinced throughout later life in the manifestations of their physiological functions. To this fact attention will be given later in more detail. The medullary part of the suprarenal gland originates in common with the abdominal sympathetic ganglia, and in the lower vertebrates these structures remain closely connected, whereas in the mammal only a few small phaeochrome bodies, the chromaffine cell masses, accompany the abdominal sympathetic chain, and almost the whole mass of cells becomes fused with the mesonephros to form, with the cortical portion, a single organ, the suprarenal gland.

In the human being, the two flattened, triangular, round-edged, semilunar bodies rest upon the upper poles of the kidneys, with whose fibrous capsule they are somewhat closely connected. The weight of each suprarenal at birth is about 6 grams, in the adult it weighs 11 to 18 grams; its length is 4 to 5 centimeters; its width, 2 to 3 centimeters; its thickness, 3 to 6 centimeters.

Histologic examination shows the cortex to consist of a number of radially arranged strands of cells which seem to arise from the aggregations of cells constituting the glands outermost layer (zona glomerulosa); these strands form small tapering columns (zona fasciculata), and they finally fuse into a meshwork of thin strands

(zona reticulata) that become gradually lost among the cells of the medullary portion. The cells of each part, cortical and medullary, differ very decidedly from one another in their staining characteristics. The cortical cells in fresh preparations stain readily with fat-staining dyes and with osmic acid; they appear brown because of the light-colored, light-refracting globules that they contain, particles which are thought to be of lipoid character on account of the manner in which they stain; the medullary cells have a great affinity for chromic acid and its salts. This staining peculiarity is also characteristic of all the similar cell accumulations that accompany the sympathetic nerve plexus in the abdomen, masses called paraganglia. These paraganglia and the medullary portion of the suprarenal, all having a common embryonic origin, are known as the chromaffine system. To this system must be added the carotid gland, which represents but a larger collection of chromaffine cells, and, in the human body, is placed at the bifurcation of the common carotid artery; this gland is 5 to 7 millimeters long, 1 to 5 millimeters thick and is richly supplied with non-medullated nerve fibres and blood vessels.

A number of minute organs similar in structure to the suprarenals are found scattered about in various places and are known as accessory suprarenals; they lie in the peritoneal cavity, within the kidney tissue, in the pelvis, in the lateral ligaments of the ovary, in the testicle and epididymis of the male.

In cases of adrenalectomy and in adrenal hypofunction

these accessory organs have frequently been found hyper-plastic.

The vascular supply is common to both the epithelial and chromaffine parts of the gland; the smaller branches of the suprarenal artery and branches from the neighboring blood vessels form within the capsule and the outermost cortical portion a very thick capillary network. Some of these capillaries coalesce to form small venules which then take their course through the medullary portion, while other capillaries penetrate the capsule to form venules which unite with the renal vein, the vena cava and the phrenic vein. The medullary portion is, also, in addition to these arteries, supplied by the small suprarenal medullary artery. The central adrenal vein is characterized by a specially developed layer of longitudinal muscle fibres in which contractions bring about a very rapid emptying of suprarenal venous blood.

The nerve filaments which are derived from the sympathetic system penetrate the medullary portion of the suprarenal and branch out to form a very fine, dense network, embracing each and every chromaffine cell and terminating in small bulbar thickenings, thus assuring an especially intimate contact with the cell proper. This unusually rich nerve supply has not been observed in the first few months of life; the cortical portion then exceeds the medullary portion in volume, but as life advances the relative size of these two divisions of the suprarenal gland changes in favor of the medulla, the ratio of cortex to medulla mass changing from 2:1 to

1:2. The accessory chromaffine cell collections already mentioned diminish in volume with advancing age, and are found only from about the fifth to the eighth year.

The fine chromaffine granules observed within the cells are regarded as precursors of the medullary hormone, adrenalin; they stain green with iron chloride and show a chromic acid affinity. They find their way directly into the blood current.

The Hypophysis (*Glandula pituitaria*)

The hypophysis is the third of the true endocrine glands which originate from more than one source. But while the individual constituents of the suprarenal gland fuse together in the course of development this fusion does not occur in the hypophysis. In the lower vertebrates differentiation between the epithelial and glious portions of the hypophysis is not yet accomplished; in these the pituitary is still a simple mixture of gland tubules and nervous tissue. But in mammals there is a complete and very distinct separation between these two tissues; in microscopic sections the three parts of the organ, the anterior, middle and posterior lobes, are easily distinguishable.

Like the thyroid, the anterior lobe originates from a pouch-like projection of the epithelial layer of the stomodeum and hence is of ectodermal origin. This diverticular pouch extends upward in front of the cephalic end of the notochord and upon reaching the dorsal portion, which projects downward from the midbrain and which later constitutes the posterior lobe, its

stalk becomes constricted, leaving a closed epithelial sac isolated from its place of origin in the stomodeum. Into the interior of this pouch protrude groups of cells proliferating from its walls and forming single strands which become separated from each other by ingrowing meso-

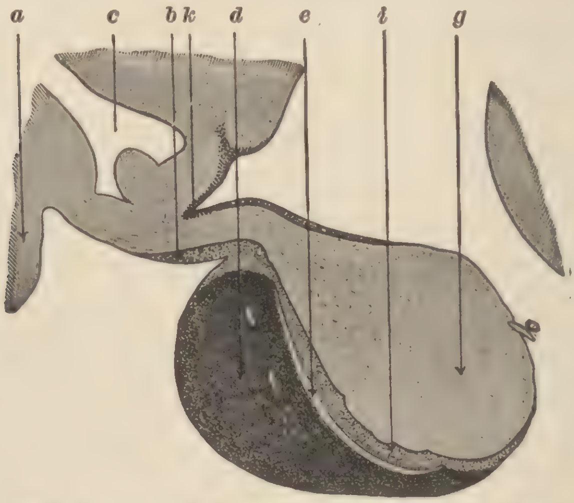


FIG. 5. Sagittal section through the infundibulum and the hypophysis of an adult ape; partly diagrammatic (Herring). *a*, optic chiasm; *b*, tongue-like protuberance; *c*, third ventricle; *d*, anterior lobe; *e*, ventricle of the hypophysis; *g*, posterior lobe; *i*, mid-lobe; *k*, portion of the mid-lobe.

dermal stroma carrying an abundance of blood vessels; the original lumen becomes more and more constricted by the encroachment of ingrowing tissues until only a narrow slit, lined in its caudal aspect by a single thin layer of epithelium, remains at the junction between the anterior and middle lobes.

In the lower mammals there lies between the anterior

and posterior lobes a wide band composed of larger cylindrical cells and designated as the middle pituitary lobe. In some animal species this cellular layer embraces the posterior lobe in its whole circumference, whereas in the human being it is stunted and forms only a small, narrow zone, invaded here and there by minute, hollow spaces filled with a colloid material. This part is known as the medullary portion or middle lobe.

The posterior lobe originates from the base of the mid-brain; from there, like the anterior lobe, it projects downward in the form of a hollow diverticular pouch lined with medullary epithelium. A dense network of fibres is sent from the base of the mid-brain into the interior of the hollow tubule, so that the posterior lobe becomes converted into a solid mass of glia tissue connected with the base of the brain by a stalk, into the upper end of which part of the infundibulum of the floor of the 3rd ventricle projects. In the dense meshwork of nerve fibres lie many large cells, supplied with processes and filled with greenish-yellow coloring matter.

A stained microscopic preparation of the pituitary shows a most marked difference between the anterior and the posterior lobes. The former contains a most varied assortment of cells, basophile cells, acidophile cells, and some, called chief cells (Hauptzellen), which assume no definite coloring with either acid or basic stains. The middle lobe contains principally basophile cells. The question whether the three varieties of cells in the anterior lobe are of different origins has at present receded to the background, inasmuch as they are now supposed

to represent only different stages in the specific functioning of the same cell; the stained granules of their protoplasm, as well as the granules found in the gelatinous mass of the posterior lobe, are presumably precursors of the internal secretion itself.

The secretions of the anterior lobe pass directly into the blood current without having to take their course through the posterior division; the latter pours its active substances into the third ventricle.

The hypophysis of man lies at the base of the skull and fills the sella turcica, which is lined with dura mater. It weighs on the average 0.5 grams, measures about 14 millimeters in its transverse diameter, 2.15 millimeters in thickness and 5.5 millimeters in length.

The Pancreas (*Abdominal salivary gland*)

Whereas in the thyroid, the thymus, the parathyroid, and the anterior pituitary gland their original functions as diverticular excretory glands of the embryonal gut are replaced in the course of development by internal secretory functions, the pancreas preserves its external secretory function, exercising this through its glandular tubules, and, in addition, it assumes an incretory rôle that is performed by certain groups of cells that lie between the glandular tubules—the islands of Langerhans. The pancreas thus presents a mixture of two glands with two different types of functioning, one an internal secretory function concerned with the general body metabolism, the other an external secretory function acting in the digestion of food.

The acinous cells, as well as those of the islands of Langerhans, originate as an outgrowth from the germ layer which forms the wall of the primitive duodenum. Because of this common origin some investigators have thought that one type of cell, engaged in a special

FIG. 6. Pancreas of a 67-year-old woman with diabetes (about $\times$ 35). *L. I.*, Islands of Langerhans, showing sclerotic degeneration; *L. I. h.*, Island of Langerhans, showing hyaline degeneration (Heiberg).

function, may be transformed into another type with a different function (Laguesse, Saguchi). Such a transformation, however, does not take place; each of these two varieties of cells performs its own task. Evidence of this is seen in the fact that glycogen production in the

embryonic liver begins only when (in man the fourth month) the primitive island epithelium of the pancreas becomes replaced by the final or permanent form of epithelium (Aron). An indication of the difference in function of the two kinds of pancreas cells is likewise seen in their different reaction to neutral gentian violet; in a section of pancreas hardened in chromium sublimate, gentian violet stains the granules of the acinous cells reddish brown, whereas those of the islands are stained dark blue (Kirkbride). Additional evidence of the difference in character of the two pancreatic cell groups is also shown by the fact that in diabetes mellitus, a disturbance of carbohydrate metabolism, the island cells often show some particular abnormality, whereas the acinous cells present no evidence of disorder. On the other hand, when the excretory duct of the pancreas is ligated the cells of the acini atrophy, while the island cells, on the contrary, proliferate, and the internal secretory function of the organ is not disturbed. Even the morphologic structure of the islands, which are built on the pattern of the parathyroid, with strands of spherical cells clustered together and separated by wide capillaries, is an indication that the islands are endowed with functions different from those of the neighboring acinous tubules. The histological difference between the finely granular protoplasm of the acinous cells is also a good indication of a difference in function.

The diameter of an island is about 0.3 millimeters; the total mass of the Langerhans islands in a pancreas constitutes from about one one-hundredth to one-thirtieth

of the whole gland parenchyma; hence, the mass of island cells, if segregated into a separate organ, would in itself form a serviceable gland, a fact which would if need be strengthen the overwhelming evidence that the cells of the islets carry on a special secretory function.

The Germ Glands (*Testis, Ovarium*)

Testicles—The testicles also represents a combination of an external and internal secretory gland, but an exceptional one in that the product poured out through its ducts is not an ordinary liquid but a fluid containing formed elements. Embryologically, the generative portion of the testicles, the seminal canaliculi (*tubuli seminiferi*), originates directly from the germinal epithelium, while the tubuli recti and the rete testis are derived from the primitive kidney, the pronephros. The numerous epitheloid cells, known as Leydig cells, that are found sprinkled within the interstices of the connective tissue which fills the spaces between the individual seminal tubules, are also derived from vestiges of the primitive kidney duct. These extra-genital portions, the Leydig cells, make up what is termed the interstitial gland. (Bouin and Ancel), or puberty gland (Steinach), and to their secretion the actual endocrine function of the testes is ascribed. The cells measure about 10 to 20 microns; their protoplasm contains crystalline substances, lipoids, and some pigment; the cells are usually arranged in rather large groups which are richly supplied with blood vessels and possess a special connective tissue meshwork of their own.

Just as it happens with the pancreas that the acinous cells atrophy and the island cells proliferate when its excretory duct is ligated, so also with the testicles, when the vas deferens is ligated an exuberant growth of Leydig cells and an atrophy of the seminal canaliculi takes

FIG. 7. Normal testis of an adult man (about $\times$ 150). *S.K.*, seminiferous tubules; *J.* interstitial cells (Steinach).

place. These phenomena also occur in cryptorchism, an imperfect descent of the testicles; in this defect of development we find the interstitial tissue fully developed, while the generative tissue is undeveloped and spermatogenesis is lacking. But since in these cases the secondary male characteristics are, nevertheless, perfectly developed we see in this experiment of nature a proof that

the internal secretory function of the testes is independent of the function of spermatogenesis. Interstitial cells are found in the gonads of all vertebrates (Kolmer and

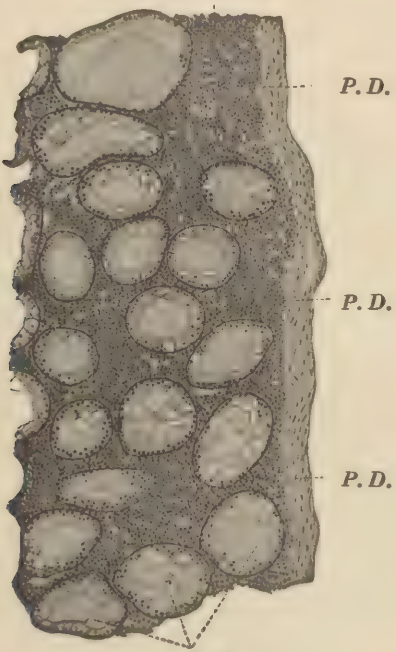


FIG. 8. **Cross-section through an eight-months old testicle graft in a guinea pig (about × 60).** ***A. G. D.***, **atrophied seminal canals;** ***P. D.***, **greatly hypertrophied "puberty gland" (Steinach).**

Scheminsky, Courrier) where they perform functions analogous to those which belong to them in human beings; in some of the urodeles, coincident with the formation of the "wedding dress" there is developed within the gonads

an immense, fat-containing, glandular tissue mass; if this is artificially destroyed the wedding dress also retrogresses.

Ovaries—The female generative glands also represent a mixture of different germ-layers. From the germinal

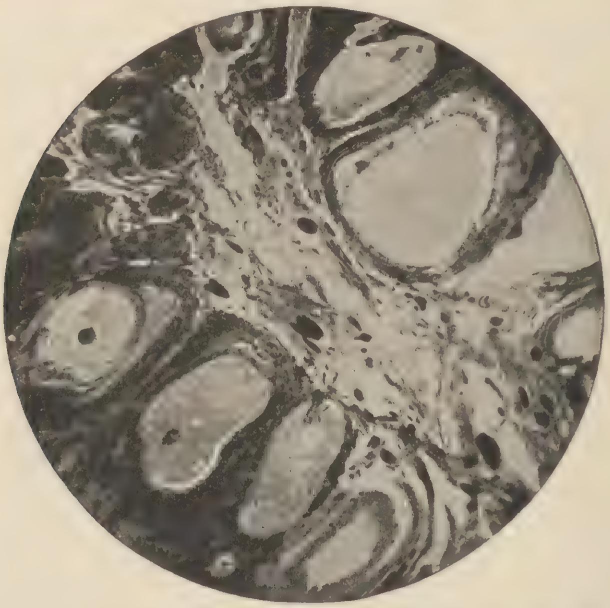


Fig. 9. Ovary of cat. Microphotograph. Eyepiece No. 2; lens AA (Zeiss).

epithelium elongated cell strands ana cell clusters, called the egg strings and egg masses, branch out; these consist of two varieties of cells, follicle cells and primitive ova. The latter become arranged in rather large groups in which all cells but one, the ovum, finally disappear; in the meantime the follicle cells form a spherical zone

around the ovum, creating the primary follicle; this becomes isolated from the neighboring follicles by the growth of interposing embryonal connective tissue which forms a special membrane, the theca folliculi, around each follicle.

In both ovaries of a woman 22 years old, one weighing 8.11 grams, and the other 5.85 grams, Haeggstroem counted more than 400,000 non-atresic follicles; 219 of these had a diameter of more than 100 microns; 1,700 had reached the stage of four epithelial stratifications; only 200 contained a fluid substance. There were five follicles with two ova each, and about 1,000 ova containing two nuclei. The number of atresic follicles and of corpora candicantia was about 12,000. Of these 54 had a diameter of 1 millimeter or more. In the larger ovary he found four corpora lutea; in the smaller, five.

With progressive ripening of the ovum the originally flattened follicular epithelium becomes more cuboidal in shape and proliferates to form several concentrically placed layers, which, as the *cumulus ovigerus,* encircle the ovum; within the follicle there accumulates a liquid which gradually fills and dilates the hollow interior, thus completing a Graafian or secondary follicle. When ripe (in the human species having grown to a diameter of about 5 millimeters) the follicle bursts and empties itself, throwing the contained ovum into the peritoneal cavity; the ovum then reaches the uterus through the Fallopian tubes. The ruptured follicle cavity becomes filled with blood, and the coagulum becomes invaded by a growth of cells from the follicle itself and from the theca folliculi.

After a time these immigrant cells degenerate and, together with the fibrous tissue supporting the blood vessels and the numerous white blood corpuscles, they form the corpus luteum, or yellow body. If the expelled ovum becomes fertilized the little yellow mass, now called the corpus luteum graviditatis, continues to increase in size by additional cell proliferation and degeneration, and by

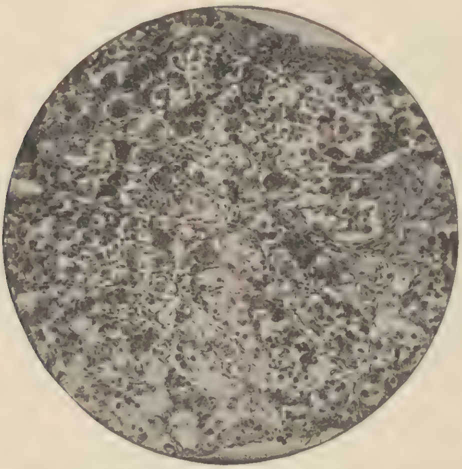


Fig. 10. Ovary of a new-born child. Microphotograph. Eyepiece No. 2; lens AA (Zeiss).

enlargement of each of the constituent cells which now contain within their protoplasm distinctly recognizable particles of a specific character (lutein). The maximum size of the corpus luteum is reached at about the fourth month of gestation, but from this period a retrogression begins; the enlarged cell masses begin to shrink and their content becomes absorbed; the process continues until only a fibrous scar remains. When impregnation does not

occur a yellow body is formed in the same manner as the corpus luteum graviditatis; but it never reaches the size and complexity of the former, and it disappears very early. If the ripe Graafian follicle does not rupture it undergoes degeneration by an immense growth of the inner layer of the theca folliculi which fills the hollow cavity of the follicle with desquamated epithelium.

We regard as the incretory part of the human ovary not only the various corpora lutea, but also these atretic follicles, the corpora lutea atretica. These are composed mainly of greatly multiplied inner cells of the theca folliculi, and differ from the yellow bodies, which are made up of various sorts of cells (theca- and granulosa- lutein cells).

The structure of the ovary in lower mammals, in the rodents, for instance, differs from the structure of the human ovary. In the rodents we find compact strands of cells which permeate the stroma of the ovaries and fill the spaces between the follicles; these correspond to the male Leydig cell interstitial tissue of the testis. In human beings, such large accumulations of interstitial cells also exist, but only before puberty (illustration 10). The cell accumulations which are found in the mature woman and during pregnancy, and which are interpreted by various investigators as interstitial glandular tissue, are, according to Simon, only atretic follicles, which have never united into compact solid masses, but have remained isolated nests of interstitial cells.

CHAPTER III

PHYSIOLOGY OF THE BLOOD

In the normal human body the composition of the blood is constant within very narrow limits, both in the number of its formed elements and in its chemical composition. Ordinarily, in studying the blood we are, for the most part, satisfied to determine the average figures for the number of blood cells, to analyze the phenomena of coagulation and to make chemical investigations of the separate components of the plasma. But we do not, by all these direct procedures, attain a nearer approach to the elucidation of the essential causes which maintain the blood in its uniform state. Only when the normal blood picture is altered by disease does it become possible to study by indirect means the part which the glands take in maintaining the normal equilibrium of the blood; for then we are in a position to compare the blood pictures peculiar to diseased states with the known clinical symptoms and with changes in the diseased organs found at autopsy. Other means of studying the relationship of the endocrine glands to the blood are furnished by animal experimentation; also by surgical removal of an internal secretory gland and replacement of its lost functions by the injection of specific extracts or by feeding with the whole gland.

The points at which the incretions begin to regulate

the blood's composition lie in the structures where the blood cells are formed. These structures are composed of a lymphatic division consisting of the spleen and lymph nodes, in which the lymphocytes are formed, and of a myeloid division, the bone marrow, where the erythrocytes constantly increase in numbers through growth and division of pre-existing cells. If cell division is accelerated or retarded, a corresponding rise or fall in the number of blood cells takes place.

There is a physiological difference in the blood of the two sexes manifested in the number of the red blood corpuscles and the hemoglobin content. According to Naegeli, the number is four and a half millions in every cubic millimeter of woman's blood and five millions in the same amount of man's blood. That this difference is due to the influence of the germ glands is shown by the fact that in castrated male dogs the number of red cells is diminished and the hemoglobin content of the blood is also decreased. In castrated human beings and in eunuchoid states (disorders of development with atrophy of the germ gland) the hemoglobin content is often reduced to 75 percent or less.

The deficiency of hemoglobin in chlorosis is still unexplained. The most characteristic symptom in this disease is the loss of hemoglobin; this may sink to 50 or even 30 percent of the normal amount in red cells of which the number remains normal. This fall of the hemoglobin index to one-third of its normal value coincident with apparently normal numbers of red blood corpuscles shows that the disturbance affects less the

building of new cells than it does the production of hemoglobin and the iron metabolism. According to Falta, an increased activity of the ovary, occurring in this disease of early adolescence, leads to an increased production of blood cells, and eventually to exhaustion of the bone marrow. The good results which follow the use of preparations of iron indicate that the cause of the disease is connected rather with an excessive loss of iron than with a disturbance in red blood cell formation. In how far other endocrine glands, such as the suprarenal, the spleen and the thyroid, may also be inculpated in this disease is a question still unanswered.

The thyroid also plays a marked part in controlling the red blood cell picture. After the thyroid is removed, or when its functional activity is diminished through disease, as in myxoedema, extreme anemia occurs. In cases of total removal of the gland the number of red cells falls to a third of the normal. When a glycerine extract of calves' or of sheep's thyroid is injected into a normal animal the number of red cells is increased 15 percent or more; feeding the whole gland has the same effect. In these cases sections of bone marrow show engorgement of blood vessels and increased cell division.

The white blood corpuscles, like the red, are also subject to regulation by the internal secretions. But even in normal blood the numbers of the different varieties of white cells varies within wide limits (about 30 percent) and, owing to this circumstance, their numbers are often given differently by different investigators. According to Naegeli, there are about 7,000 white blood cells

in 1 cubic centimeter of blood; 65 to 70 percent of these are neutrophiles, 2 to 4 percent are eosinophiles, 0.5 percent are mast cells, 6 to 8 percent are large mononuclears and transitional forms, and 20 to 35 percent are lymphocytes.

The influence of the thyroid on the white blood cell count was first observed in Basedow's disease. In classical cases of this disease the total number of leucocytes is not appreciably changed, ranging from seven to ten thousand, but the proportion of neutrophiles to lymphocytes is altered and very different from the proportions in normal blood; there may be 41 to 66 percent of polynuclears and 51 to 26 percent of lymphocytes (computed from 52 cases by Klose, Lampé and Liesegang). This lymphocytosis often persists even after operation upon the thyroid and recovery from the disease. The altered action of the thyroid secretion is, therefore, not the sole cause of the hyperfunctioning of the lymphatic system, resulting in an excessive production of lymphocytes. The hyperplasia of the thymus which is found at autopsy in about 80 per cent of Basedow subjects indicates that the thymus and not the thyroid is the real cause of increased lymphocyte production. In children with thymus hyperplasia, but with no thyroid disease, there is also a change in the proportion of polyneuclears to lymphocytes, a change which may displace the ratio to 24:76; soon after the removal of the thymus the ratio returns to 62:37.

The lymphocytosis with a simultaneous reduction in the number of polynuclear leucocytes which occurs after ovariotomy is, according to Klose, Lampé and Liesegang,

due to the removal of the normal growth-restraining influence of the germ gland upon the thymus, in which atrophy and decreased functioning ordinarily begin at the onset of puberty. In Basedow's disease the disordered thyroid secretion acts in a manner analogous to castration or to exposure of the germ gland to X-rays, both of which lead to thymus hyperplasia. The inhibitory influence exerted on the germ gland by the thyroid hyperactivity of Basedow's disease manifests itself also in a diminished libido and impotence in both sexes and in a cessation of menstruation in woman. This physiological interdependence of the thyroid and ovary has long been known from observations of the enlargement of the thyroid during pregnancy and menstruation (see chapter VIII).

We see here one example, and others will be presented later, of the mutual reciprocity existing between glands with an internal secretion. The particular relationship which concerns the regulation of leucocyte production, may be illustrated in the following schema:

Thyroid—>Gonads—>Thymus—>Blood

The other lymphatic organ, the spleen, seems to be under the influence of the suprarenals. Within half an hour after the injection of adrenalin, there is a rise in the total number of white blood corpuscles to some 22,000 with a slight simultaneous increase in lymphocytes (Port-Brunow).

At the same time the eosinophiles become so scarce as

to practically disappear, even in cases where an artificial eosinophilia has been previously produced by the injection of extracts from intestinal parasites (*ascarides*). After a time, the polymorphonuclears increase again and the lymphocytes diminish in number. Extirpation of the spleen makes adrenalin ineffective, for after removal of the spleen adrenalin injection has no more effect on the leucocyte numbers.

Lately an antagonism has been described between the thyroid and the spleen which concerns the production of red blood cells in the bone marrow. From the older experiments it was known that, unlike the normal reaction, thyreoidectomized animals do not show any increase in the number of erythrocytes during a stay at high altitudes, even though it be a long one; neither do thyroidless animals react by an increased production of erythrocytes after injections of serum from other anemic animals—injections which in normal animals stimulate the blood-building organs to notably increased activity. According to Dubois, an artificial anemia of thyroidless animals is more difficult to overcome than an anemia of normal animals, whereas if the thyroidless animals be also splenectomized the conditions are reversed; in these an increase of hemoglobin above the normal has even been observed. Increase in the hemoglobin and the number of red cells also occurs in animals from which only the spleen has been removed.

The influence of the internal secretory glands upon the number of blood cells may be summed up as follows:

stimulation of the myeloid system is brought about through the thyroid; stimulation of the lymphatic and the myeloid systems through the adrenals; depression of the lymphatic system (thymus) through the germ glands.

TABLE I.

BLOOD PICTURES IN ENDOCRINE DISORDERS.

Disease	Red Cells Millions	White Cells Thousands	Polynuclears %	Lymphocytes %	Observer
Normal	4.5–5	7	65–70	20–25	Naegeli
Myxoedema and Thyreoprivæ	3.5	6–7	62.6	32.4	Falta
			Eosinophiles 6%		
Basedow's Disease	5.	7–10	41–66	26–51	Klose & Others
Thymus hyperplasia (Child)	5.	18	24	76	" " "
Dog, normal	7.	19	69	22	Port-Brunow
Dog, ovariotomy, after 2½ mo.	5.9	28	55	40	Klose & Others
Thirty minutes after injection of 5 mg. adrenalin	..	21.8	68 (14,700)	26 (5600)	Port-Brunow
Thirty-three hours after injection of 5 mg. adrenalin	..	41.6	89 (36,900)	9 (3900)	" "

The composition of the blood plasma, being the result of the combined action of all the cells in the body, is naturally affected by the incretions of the endocrine glands. Their control of the blood sugar content, of the inorganic salts and of the other non-colloidal substances will be dealt with in greater detail in the chapter on metabolism. Here, we shall limit our attention to the facts that are

known regarding the relations between the coagulation of blood and the endocrine glands.

According to a theory still very much debated the antecedent of the blood clot is a protein body, fibrinogen, which unites with fibrin ferment to form fibrin. The fibrin ferment, or thrombin, exists in the circulating blood plasma as prothrombin, which is activated by the calcium ions. The prothrombin is formed by two antecedents, thrombogen and thrombokinase. By modifying any of these separate factors coagulation may be either accelerated or retarded.

It is known that the parathyroids exert considerable influence upon calcium metabolism. After their removal calcium impoverishment results because this element of the ingested food can no longer be assimilated by the organism. In tetany which follows the removal of the parathyroids the coagulation time of the blood is increased because calcium, the activator of thrombin, is lacking.

The blood plates are regarded as the source of thrombokinase (Morawitz); this is presumably set free through the dissolution of the platelets during blood clotting. The place of origin of the blood plates is the bone marrow, not, as is often assumed, the spleen (Naegeli). In the spleen, a lymphatic organ, the accumulation of blood plates has often been observed; but in reality they are only retained and destroyed, but not formed there; for after the removal of the spleen their number in the blood is not affected. Lately, Stephan has described observations concerning blood coagulation; he found that coagulation

was accelerated by the addition of serum from patients whose spleen had previously been X-rayed. He believes he has showed that through such X-ray treatment a direct increase in the coagulation ferment is brought about by the reticuloendothelial part of the spleen, which he considers a true incretory tissue. But it seems possible to explain this acceleration in a simpler way, and in accordance with the investigations just described. It may be that the destruction of platelets in the spleen is inhibited by Roentgen radiation, so that the platelets increase in the blood stream and become instrumental in hastening coagulation; or the destruction of lymphocytes by means of X-rays may set free thromboplastic substance as is known to happen in the treatment of tumors (Szenes). Roentgen therapy furnishes many other examples of inhibition of organ activities, and in this particular case it seems unnecessary to assume that the spleen plays the rôle of an incretory organ in the formation of thrombin.

Diminished coagulability appears to be a physiological property of menstrual blood. Coagulation is retarded by extracts of ovaries from young women, but not from ovaries removed after the menopause. Whether in this case the substance which inhibits coagulation is furnished by the Graafian follicles, or whether the thromboplastic complex is influenced through the thyroid must be decided by future investigations According to Yamada, removal of the thyroid retards blood clotting. Blank also found delayed coagulation in 43 percent of patients with Basedow's disease—results which are interpreted as

showing an antagonistic relation between the thyroid and the spleen. The acceleration of blood clotting after removal of the spleen, which these authors describe, may, like the blood stasis in hemorrhagic diatheses and like hemolytic jaundice occurring after removal of the spleen, be explained as due to the fact that the destruction of blood platelets is lessened, and that consequently these accumulate in the blood and hasten its coagulation. Yamada's interpretation of this retarded coagulation as being due to the effect of an internal secretion produced by the spleen, seems, therefore, unnecessary, since this effect may clearly be due to the mechanical conditions as the result of spleen removal.

We may, then, summarize our present knowledge concerning the influence of the internal secretions upon blood coagulation by stating that the parathyroids indirectly favor coagulation through their influences upon calcium metabolism, and that the spleen retards coagulation through the destruction of blood plates, and not by the production of a special coagulation ferment, or hormone, which influences other organs either directly or indirectly.

The influence of the germ glands upon the composition of the blood has already been discussed. Recent determinations of the sinking velocity or, as it is called, the sedimentation rate of the red blood cells have shown a specific sex difference. In adults the red cells sink more slowly in the blood of males than of females (Fahreaus); in the pregnant woman the sinking velocity of the red blood corpuscles becomes greater toward the middle of pregnancy than it is in the normal non-pregnant

woman. It must, however, be left for future observations made after extirpation of the germ glands, to show whether these phenomena are really due to the influence of incretions which regulate the composition of blood plasma in definite ways. That influences do exist which differentiate male and female blood is also shown by differences in another property of the blood, its viscosity, the viscosity coefficient for man being 4.798 (water at 38°=1), for woman 4.516 (Determann). There are also differences in the ratio of the total blood mass to the body weight, the proportions being 1:11.5 for man and 1:13 for woman (Kottmann).

CHAPTER IV

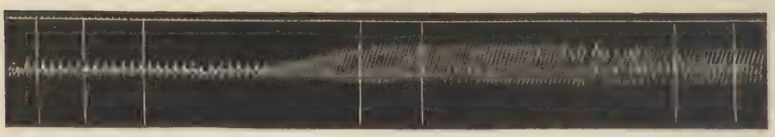
THE CIRCULATION OF THE BLOOD

The distribution of the blood in the body is dependent upon two factors: the activity of the heart and the tension of the peripheral vessels. Both of these factors are influenced by the internal secretions. The heart's activity is, in addition, regulated by two separate nerve systems; one system with automatic centers residing within the heart proper, namely, the sinus node and the atrioventricular node (Keith-Flack and Aschoff-Tawara nodes); the other system with brain centers which dominate cardiac activity through the vagus nerve and through the accelerating branch of the sympathetic.

In the living, warm-blooded animal stimulation of the vagus depresses the four fundamental functions of the heart; it decreases the rate of the beat, diminishes the size of the beat, lessens the heart's irritability toward stimuli, and reduces its conductivity for stimuli. These phenomena are technically described as negative chronotropic, negative inotropic, negative bathmotropic and negative dromotropic effects. Stimulation of the sympathetic in warm-blooded animals has the opposite effect: it induces acceleration of all the heart's activities and is, therefore, said to have effects which are positively chronotropic, positively inotropic, positively bathmotropic and

positively dromotropic. Both nerve systems of the heart, its autonomous and its peripheral nerve system, are influenced by internal secretions; of these influences the effects produced by the suprarenal hormone, adrenalin, have been studied most thoroughly.

When the heart of a surviving animal, either a warm or a cold-blooded one, is transfused with Ringer's solution to which a minute quantity of adrenalin is added, an increase in the rapidity and force of the beats may quickly be noticed. The stimulating effect of adrenalin



a *b*

Fig. 11. Curve obtained from a cat's heart perfused with diluted defibrinated blood from the same animal. Between *a* and *b* 0.3 ccm. of a 10 percent suprarenal extract was added. Within 30 seconds the heart rate had increased from 78 to 96; the height of the curve from 3.5 to 9.5 mm. (After Gotlieb).

is so intense that the intravenous administration of a fraction of a milligram may restore regular cardiac contractions even after there has been a complete stoppage of the surviving heart in diastole, as happens in cases of poisoning with potassium salts, or during chloroform or chloral hydrate narcosis.

In addition to these positive chronotropic and inotropic effects upon the heart's action adrenalin also accelerates the velocity of the heart's contraction wave and increases the irritability of the heart muscle. Normally, impulses originating within the sinus node determine the contrac-

tion rhythm of auricle and ventricle. Between the two beats a short pause occurs, for the impulse which initiates the auricular beat is delayed for a short time in the auriculoventricular bundle before it is transmitted to the muscle fibres of the ventricle. If adrenalin is added to the circulating fluid the pause is shortened; the ventricular beat follows more quickly after the beat of the auricles, so that the ventricular curve reproduced in a tracing is seen to overlap the small descending limb of the auricular curve. Adrenalin, therefore, increases conductivity for automatic impulses originating within the nodes.

The cardiac automatic centers themselves are also *directly* affected by adrenalin. If the sinus node is removed, or if its action is eliminated by cooling it with carbon dioxide crystals, a new cardiac rhythm, the atrioventricular rhythm, sets in; auricle and ventricle then contract simultaneously, their contraction impulses originating in one node only, the atrio-ventricular, and not in both nodes as is normally the case. If, in these circumstances, the isolated heart is treated with adrenalin, the rate of contraction is immediately increased, which proves that the Aschoff-Tawara node is *directly* stimulated by adrenalin to increased activity.

When the action of the suprarenal glands on the heart was first studied it was thought that the positive influence of the hormone adrénalin was exercised upon the heart muscle direct. But we have since learned that the point of attack of the suprarenal hormone is not the muscle tissue proper, but the endings of the sympathetic nerve, the contact points between the nerve and muscle

fibre, the *myo-neural junction tissue* of the English investigators (Brodie and Dixon). According to Langley, this component of the muscle cell, known as the receptive substance, is the portion which responds to chemical and nerve stimulation, and the other cell component, the *chief* substance, is only then affected through the first. The chief substance is the contractile substance and is the seat of metabolic exchanges. This assumption finds support in the fact that when the peripheral sympathetic nerve endings are excluded by means of apocodein or ergotoxin, adrenalin, even in large doses, has no longer any influence upon the muscle tissue of the surviving heart of warm-blooded animals. It has also been found that in children who have had a long previous treatment with atropin adrenalin fails to raise blood pressure, as it does in children who have not been given atropin. (Schiff and Balint.) A further proof of this view is the fact that in chick embryos 2 to 3 days old the heart, which as yet contains no sympathetic fibres, cannot be influenced to increased contraction by adrenalin; not until about the 5th to the 7th day, when the microscope shows the presence of sympathetic nerve fibres, does the heart respond to the action of adrenalin.

Proof was also sought that adrenalin has a direct effect upon the ganglion cells imbedded in the heart muscle and in support of this belief the fact was adduced that after tying the third Stannius ligature, by means of which the ganglion-cell-free apex is cut off from the rest of the heart, adrenalin is powerless to produce an apex beat, although the rest of the ventricle continues to contract.

But in this case it may be argued that no sympathetic nerve endings are present in the apex, and that the impulse to contract travels to the muscle fibres of the apex by way of the bundle of His, and that when this pathway is blocked by the ligature no contractions can take place. Another support for the theory that adrenalin acts on the endings of the sympathetic nerve is the complete correspondence of an electro-cardiogram obtained during stimulation of the accelerator nerve in a living animal with curves recording the effect of adrenalin on the surviving mammalian heart.

Notwithstanding the clearness with which the effects of adrenalin are manifest in the isolated heart of both warm and cold-blooded animals these effects cannot be shown on the heart *in vivo*. After intravenous injections of adrenalin the heart plethysmogram does not show a stronger contraction and a more rapid rate, but exactly the contrary, a diminished contraction and a retarded pulse rate. Not till 15 minutes after the intravenous injection of 0.2 milligrams of adrenalin (cats) does the volume of the cardiac contractions show an increase with regular and rapid beats (Biedl). An explanation for these seemingly paradoxical phenomena may be found in the reflex excitation of the vagus center caused by the increased blood pressure brought about by the adrenalin injection; for if this increased vagus activity is excluded by the section of the nerve, or by the administration of atropin, the accelerating action of adrenalin begins immediately after its injection.

Just as the suprarenal medulla yields a specific sub-

stance, adrenalin, so does the suprarenal cortex yield large amounts of a specific substance, cholin. The action of cholin upon the heart is exactly opposite to the action of adrenalin; it acts on the inhibitory fibres of the vagus and, therefore, slows the rate of the beat; it diminishes the size of the heart's contractions, decreases its conductivity and decreases its receptivity for stimuli. But cholin is not, like adrenalin, a specific product of chrom-

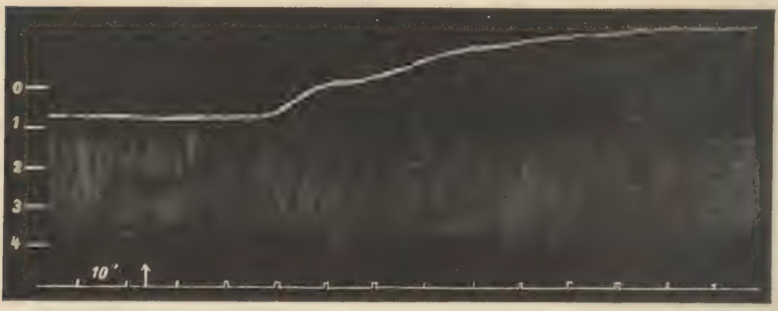


FIG. 12. Plethysmogram of a rabbit's heart receiving an infusion of 0.0032 mg. of adrenalin per minute and per kilogram of body weight. Soon after the beginning of the infusion a small decrease in volume and a fall in the rate, from 230 to 220 per minute, takes place. The upper line shows the blood pressure curve registered by a mercury manometer. (Trendelenburg.)

affine tissue and is not confined to it exclusively; it is found also in other organs, the spleen, pancreas, liver, muscles, kidneys and lungs.

The hypophysis also produces a secretion which affects the heart. Fresh extracts of the middle lobe, which may easily be prepared from ox glands, and pituitrin, a preparation made from the mid-lobe extract, diminish the rate of the heart's contraction, but increase the force of each individual systole and diastole. When these products are

added to the perfusion fluid of a surviving heart, the results are independent of the concentration, occurring in dilutions of 1 : 10,000 as well as in dilutions of 1 : 300; the same results are also obtained in the living animal. The reduction of the pulse rate is, in this case, not caused by the effect of the hypophysis preparation upon the vagus, since it also occurs after section of both vagi, but the action is exerted on the heart muscle itself. In the frog's heart, increase in the volume of the beat has been obtained with hypophysis optones, *i.e.*, completely autolyzed gland products (Abderhalden and Gelhorn), but these did not produce the typical slowing of the beat obtained with extracts of the hypophyseal mid-lobe.

According to Schickele, extracts of the whole pituitary gland behave differently from extracts of the middle lobe or from pituitrin. It seems that in the extract of the whole gland there may be various hormones which have an antagonistic effect upon one another, for alcoholic extracts of the anterior lobe alone also induce slowing of the pulse rate with a simultaneous increase in the force of the beat, like extracts of the middle and posterior lobes.

Besides their important action upon the heart's contraction adrenalin and hypophysis preparations also take an active part in the regulation of blood pressure. The increased blood pressure which these hormones produce is not only the result of the strengthened cardiac contractions, but it is also due to their direct effect upon the smooth muscle fibres of the blood vessels. These incretions stimulate the vascular muscle fibres to in-

creased contraction, thereby narrowing the lumen of the arterioles and producing a general increase in resistance within the vascular system. The vaso-constrictor fibres, with the exception of those supplying the coronary vessels of the heart and the buccal mucous membrane, take their course in sympathetic nerve trunks; they originate principally in the thoracic division of the spinal cord. The antagonistic vaso-dilators often run in the same nerve trunks, but they arise from other roots of the spinal cord and belong mostly to the para-sympathetic system, which takes its origin in the mid-brain, the medulla oblongata and the sacral cord.

In harmony with its action on the sympathetic nerve endings in the heart is the action of adrenalin on the endings of the vaso-constrictor nerve fibres, fibres derived also from the sympathetic. The effects of adrenalin on the sympathetic system can be shown by many experiments and particularly well upon decerebrated cats. Such animals react easily to adrenalin and enable one to observe its effects without any inhibiting influences from the brain. The most common object used for experimentation with adrenalin, is the Laewen-Trendelenburg frog-blood-vessel preparation. In a beheaded frog the abdominal aorta and vena cava are cut and fine glass canulas inserted into them. The aorta is then connected through its canula with an elevated Marriotte's flask containing Ringer's solution in which the constant liquid pressure maintains a steady flow through the blood vessels, causing about 30 to 40 drops per minute to fall from the venous canula when a medium-sized Rana esculenta

is used. When adrenalin is added to the perfusion liquid the number of outflow drops per minute immediately diminishes, thus proving that the vessels have contracted. By this means it is possible to determine the presence of adrenalin in solutions of as great a dilution as one

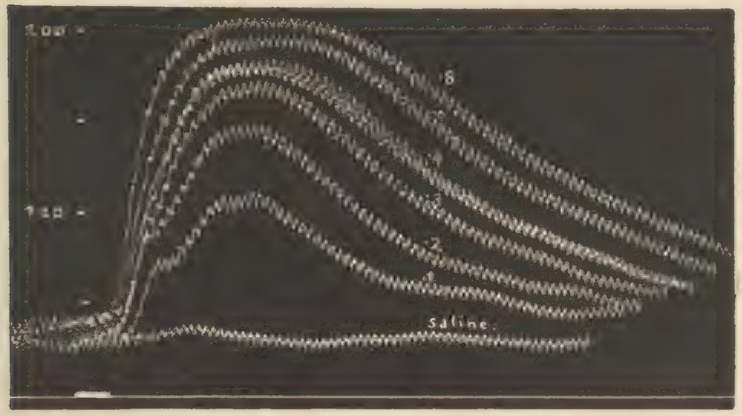


FIG. 13. Blood pressure measured in the cartotil of a decebrated cat. showing an increased pressure proportional to the injected quantity of adrenalin of a standard solution of 0.0025 percent. Lower curve given by a sodium chloride solution, shows no effect upon blood pressure; higher curves given by injections of 0.1, 0.2, 0.3, 0.4, 0.6 and 0.8 ccm. adrenalin solution, after which an injection of 0.4 ccm. gives a curve superimposed on the former 0.4 ccm. curve. The ordinates give the blood pressures measured in millimeter of mercury. (Elliot.)

to four hundred millions (Trendelenburg), or in quantities containing 0.0000025 milligrams in 1 cubic centimeter.

Trendelenburg found that both suprarenals in a rabbit gave each minute about 0.0002 milligrams of adrenalin for each kilo of body weight, making its concentration in the circulating blood about 1 part in 1,000 millions. This amount of adrenalin is insufficient to produce a rise in blood pressure, for which an output into the blood of

0.001 to 0.0005 milligrams per minute and kilo of body weight is necessary. Trendelenburg therefore believes that the property of maintaining a constant muscle tonus of the blood vessels, which is attributed by other authors to adrenalin, does not actually belong to it.

In the living organism, however, the case is somewhat different; here the adrenalin action is reinforced and enhanced by various other hormones (pituitary, thyroid) so that it *is* possible that in these circumstances the quantity of adrenalin sufficient to keep the smooth muscles in a definite, continuous state of tension may be much smaller than is required for this purpose in an animal experiment, where adrenalin alone is used. Even if it be admitted, that in the living organism the adrenalin concentration alone is inadequate to produce the blood vessel tension, the action of adrenalin may be explained by assuming that it performs the task of increasing the irritability of the sympathetic nerve endings for central and peripheral stimuli. Such an effect has already been exemplified by the action of thyroid preparations on the vagus. That adrenalin alone does not directly and exclusively maintain vascular tonus, is seen, however, in the fact that after the removal of the suprarenals the fall of blood pressure is gradual and not sudden, and that a complete loss of vascular tonus does not occur. The greater rapidity with which this fall of blood pressure occurs in decerebrized cats points to the cerebral cortex as having a simultaneous action on blood pressure. To use a rough comparison one may imagine the small, physiologically active quantity of adrenalin as acting like

some kind of lubricating medium, reducing at the myoneural junction the resistance which the muscle protoplasm offers to the stream of stimuli coming from the sympathetic.

Oswald has demonstrated a direct increase in the nervous irritability of vaso-motor muscles induced by another hormone, an iodine containing protein substance obtained from the thyroid and known as iodothyreoglobulin. When he stimulated the exposed vagus nerve of a narcotized cat by an induction current, with the secondary coil at a distance of 175 millimeters, the blood pressure sank 15 millimeters; if he then injected 30 cubic centimeters of a 2.5 percent solution of iodothyreoglobulin he obtained, with the same current strength, a 33 millimeter fall in blood pressure. At the same time he also noticed an increased responsiveness of the sympathetic nerve. When he injected a rabbit weighing 2,750 grams, with one-half a cubic centimeter of adrenalin solution (1:1,000) he found an increase in blood pressure from 36 to 42 millimeters of mercury, lasting 55 to 75 minutes; but after injecting 6 cubic centimeters of a thyreoglobulin solution the blood pressure rose from 40 to 56 millimeters for 80 to 107 minutes. The same effects were also observed when whole thyroid gland substance was fed to animals(Santesson).

This non-specific action of thyroid substances on various nerves also explains the heightened irritability observed in human beings suffering from Basedow's disease, or in those fed to excess with thyroid extracts; it also explains the opposite situation, the diminished re-

sponsiveness to nervous stimuli of persons, from whom the thyroid has been removed; and the stupid behavior and appearance, with decreased mental acuity, seen in sufferers from myxoedema and other forms of thyroid hypofunction.

Lack of adrenalin results in a marked lowering of blood

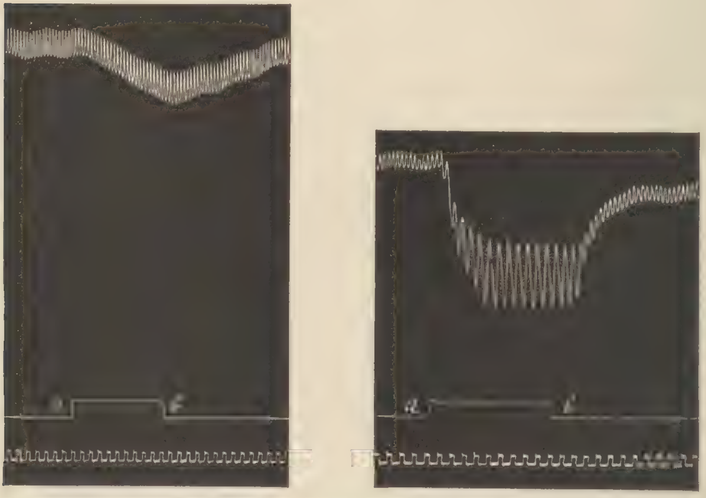


FIG. 14. Effect in blood pressure produced in a cat by vagus stimulation before and after injection of iodothyreoglobulin. Left, before; right, after injection. Nerve stimulated between *a* and *b*. (Oswald.)

pressure, as we saw in the cases of suprarenal removal already spoken of. In human beings the clinical picture of a low blood pressure is seen in Addison's disease and in individual cases of congenital, subnormal development of the suprarenals. After removal of the germ glands the blood pressure also falls, but whether this is due to loss of the gonad hormone, or to the hypofunctioning of

the suprarenals which always accompanies the removal of the germ glands, is not yet certain. It is true that a rise of blood pressure is caused by the injection of germ gland extracts, but this cannot be regarded as proof of a blood-pressure-raising property of these extracts; the rise may, as many believe, be due to intracapillary coagulation phenomena.

Increased adrenalin action, such as follows artificial stimulation of the splanchnic nerves, or an increase in impulses of central origin, should also alter the distribution of the blood in the various regions, since more powerful contractions of the muscles of the arterioles would result especially in a driving of the blood out of the capillaries. The arteries of the skin, kidney, liver and mucous membranes, especially the mucosa of the nose, are particularly sensitive to the smallest doses of adrenalin, whereas the vessels of the brain, the lungs, the extremities and the coronary arteries are less easily stimulated. Therefore, whenever the adrenalin output is increased, the blood is diverted from the skin and the large abdominal viscera and is directed to the brain, the limbs and the coronary arteries.

Hypophyseal preparations have an action that is the opposite of adrenalin action on certain vascular regions; this is especially true of the arteries of the kidney, which they cause to dilate. It was thought for a long time that the secretions of the pituitary stimulate the vagus and the para-sympathetic system, and that they were, in this regard, antagonistic to the sympathetic nerve. But as the action of pituitary hormones continues even when

both vagi are divided it must be assumed that the action of these secretions on the heart and the muscles of the blood vessels is a direct one.

Another such direct effect of pituitary preparations upon smooth muscle tissue will be considered later in connection with the uterus.

Certain definite injuries have been produced in the blood vessels of animals treated by frequent administrations of large doses of adrenalin. After repeated injections of 0.001 milligrams of this hormone small, pin-head size, white spots have been found in the intima of the larger vessels, especially of the aorta. These indices of disease of the vessel wall prove on histological examination to be patches of cell degeneration, with fatty necrosis and calcification of the intima; the muscular and elastic tissues of the wall also show injury. The arterial changes, atheroma, observed in experimental animals are ascribable to mechanical causes, principally to the greatly increased (more than doubled) pressure in the main arteries, brought about by contraction of the peripheral arterioles as the result of adrenalin injections. (Leersum and Rasses.) How far these changes may also be due to the chemical action of the adrenalin itself is not yet positively known.

Such pathological changes of the arterial walls are also seen in the vessels of the aged and in diseases characterized by an abnormally high blood pressure. Therefore, it may easily be supposed that these conditions are due to a continuous, persistently augmented adrenal activity during the life of the person so affected.

The effect of the internal secretions upon the circulation may be summarized as follows: the adrenals and the thyroid influence the muscles of the heart and blood vessels indirectly, through an increase in the irritability of their sympathetic nerve terminals; the hypophysis acts on the cardiac and arterial muscles directly.

CHAPTER V

RESPIRATION AND VOICE PRODUCTION

Whereas adrenalin causes an increase in tension of the muscles of the vascular system it induces, even in dilutions of one part to three millions, a decrease of tension or a relaxation of the delicate smooth muscle fibres of the bronchioles. This property of adrenalin has been made use of in the treatment of disorders with increased tension of the bronchioles, as in asthma, for example.

This apparently paradoxical behavior of adrenalin, in producing opposite effects upon two sets of smooth muscles, is explained by the experimental results obtained through stimulation of the cervical sympathetic nerve. Electrical stimulation of the cervical sympathetic produces a diminished tonus of the bronchial muscles, whereas stimulation of the vagus increases their tonus. The action of adrenalin, therefore, is, in both cases, identical with the results of sympathetic stimulation.

Another example of such depression of muscle tonus is shown in the effect of adrenalin upon a strip of surviving œsophageal muscle. Such a strip, suspended in Ringer's solution, ceases to contract as soon as adrenalin is added, just as the œsophageal muscles do in a living animal when the sympathetic nerve is stimulated. Thyroid extract has the opposite effect on bronchial musculature;

it increases the tone of the bronchial muscles and thus narrows the lumen of the bronchi.

To adrenalin there has also been ascribed a direct action on the respiratory center in the medulla, because after its injection into a vein the respirations become more and more shallow; they gradually grow slower until, after large doses, respiration comes altogether to a standstill. But these phenomena can be completely explained as the result of a decreased stimulation of the respiratory center caused by the diminished carbon dioxide content of the blood supplying the center. This diminution in the blood carbon dioxide after adrenalin injection is the result of an increased blood supply, and a consequent better aëration of the whole brain, including the respiratory center. The slowing and flattening of respiratory movements up to the point of standstill which is produced by injections of pituitrin may be explained in the same way, without assuming for this drug a direct action on the endings of the respiratory nerves.

The pitch of the voice is dependent upon the length and tension of the vocal cords, and the form of these is determined by the structure of the larynx. The normal male larynx is 7 centimeters high in its anterior diameter, its greatest width is 3 centimeters, and its depth at the lower border of the thyroid cartilage is 3 centimeters. In women, the corresponding measurements are 4.8 centimeters, 3.5 centimeters and 2.4 centimeters. The male glottis is on the average 2.5 centimeters long, the female, 1.5 centimeters. These sex differences are not developed

until puberty, as until then the larynx of male and female children grows at the same rate.

But at puberty the glottis of the boy's larynx begins to lengthen very rapidly, so that in about a year it reaches nearly double its original length; the girl's glottis continues its slow progress and reaches during the same period only one and a half times its former size. The changes in the laryngeal structure of the boy are the cause of voice mutation during his puberty period. With advancing age the cartilaginous larynx begins to calcify and its muscles to atrophy, so that at the age of 50 to 60 another mutation of the voice occurs, producing the voice of old age.

That these puberty changes in the boy's voice are induced by the male gonads is shown by the absence of voice changes in boys castrated before puberty. In these the larynx continues to grow, but not so rapidly as in the normal male; it also fails to ossify and its relative smallness in the large oral cavity of the commonly overgrown eunuch gives to his voice an especially great resonance; its pitch remains high as in the child. Advantage was formerly taken of these conditions to obtain male soprano singers. This custom persisted even down to the thirties of the nineteenth century as a means of retaining soprano voices in adult singers of the Papal choir. Mutilation of the testicles, such as is frequent in war, also causes the voice to become of a higher pitch; successful implantation of new testicles produces a return of the normal voice. (Lichtenstern.)

Statistical investigations made by Bernstein and

Schlaeper showed that of 1,061 men's voices 188 were tenor and 873 bass; of 1,035 female voices 151 were alto and 864 soprano; therefore, about 82 percent of men and 84 percent of women possess a voice specific of their sex. Gigon found that 75 percent of all soldiers who retained their infantile voice pitch (32 in 575 recruits) showed, in addition, a defective development of body hair.

The development of the thorax plays a most important rôle in the volume of the voice. In men of 30 to 40 years the measurement of the chest at the end of expiration averages 82 centimeters; in women 76 centimeters. Castrated males usually show a flattening of the thorax, thus approximating the female form of chest.

In the lower animals the pitch and compass of the voice also depend upon the germ glands. In the cock, for example, the voice is musical; in the capon, the castrated cock, the voice is cracked. In frogs, Rana esculenta and Rana fusca, the voice of the male is very much more powerful than that of the female; it is louder and more voluminous because of the larger and more powerful belly muscles and the possession of a special sounding sac.

These examples serve to introduce us to the influence of the endocrine glands on the growth and form of the body, and they furnish additional instances of the indirect rôle that these glands play in carrying on the physiological functions of the separate organs.

CHAPTER VI

METABOLISM

1. *Metabolism of Gases and Heat Regulation*

The theory which was held until lately in regard to the nervous correlation of organs assumed that the various functions of the organism which must coöperate in order to keep the body of the warm-blooded animal at a constant temperature had each to be regulated from separate brain centers. It was thought that the oxidation pro cesses within every cell, the rapidity of the blood circulation, the size of the cutaneous blood vessels, the activity of the sweat glands—conditions all closely connected with bodily heat—were directed by the brain. More extended conceptions attributed all these activities to a special heat center, located in the regio subthalamica, the tuber cinereum (Krehl, Isenschmid and others), or even to two centers, one for heat, the other for cold (H. H. Meyer).

But very numerous experimental findings and clinical observations have shown that the glands of internal secretion exert an influence on heat production. After removal of the thyroid, for instance, a fall of one to two degrees in temperature takes place; in myxoedema, a hypofunctioning of the thyroid, rectal temperatures in the affected subjects may register less than 36° C., whereas in

Basedow's disease, a thyroid hyperfunctioning, a decided rise of body temperature has been observed.

After excision of the parathyroids the experimental animals lose, to some extent, the capacity to regulate their body temperature. They become partly poikilothermous; if the surrounding temperature is raised three or four degrees, the animal's temperature may rise to nearly the same extent. A similar reaction to an increase in the surrounding heat takes place in thyroidless rabbits; normal animals kept in a warm chamber react with quickened respiration, thus providing for heat stabilization; those from which the thyroid has been removed show no increased respiratory rate for some time after the operation, and, consequently, their temperature rises. Removal of the adrenals is also associated with a marked fall of body temperature, whereas after injection of 0.2 milligrams of adrenalin, a rise of 0.6° C. has been observed.

The question therefore arises whether all these manifestations are to be ascribed to the influence of hormones upon the heat center, or whether there are not, perhaps, other explanations for these phenomena? The principal source of animal heat production is, as already mentioned, the oxidation processes within the body cells; an external measure of these combustion processes is the amount of oxygen inhaled and the amount of carbon dioxide exhaled. If the outer temperature falls, more oxygen is consumed and more carbon dioxide expelled. There are now reported numerous investigations showing that after removal of the thyroid, or of the pituitary or

of the testes, the oxygen consumption and carbon dioxide elimination may be reduced to 30 percent of the normal values, and that the administration of extracts or other preparations of the removed glands will help to neutralize this lessened oxidation.

Nature performs the same experiment in hibernating animals; during hibernation the metabolic exchange of gases is reduced to the minimum; the body temperature of these animals corresponds to that of their surroundings; the thyroid and the hypophysis assume an atrophic state; their histological pictures show a shrinking of the colloid substances and a decrease of follicular cells with changes in the staining qualities. (Cushing and Goetsch.) Upon awakening in warmer surroundings the temperature of hibernating animals rises rapidly to the normal; in a shrew, the temperature rose from 8° to 32° C. in two or three hours, rising in the last 40 minutes alone from 21° to 32°. The same sudden elevation of temperature with increase in respiratory rate was observed by Adler in hibernating bats and porcupines after he had injected them with extracts of thyroid or with adrenalin or certain proteinogenous amins. These elevations of temperature occurred not only in normal animals, but also in those in which participation of the heat regulating center had previously been excluded by section of the spinal cord, or by paralysis of the sympathetic nervous system with ergotoxin. He concluded from these investigations that when oxidation processes are stimulated by incretions the point of attack is not a brain center, but the body cells themselves. This view is also

supported by the findings of Mansfeld and Pap, who showed that the surviving heart from a thyroidless animal was less able to utilize sugar than the surviving heart from a normal animal; they deduced from this that the thyroid secretion controls the chemical regulation of heat directly through its effect upon cell oxidation. In this connection the observations of Schenk should also be mentioned; he found that injecting thyroidless rabbits with the serum of chilled normal animals caused the temperature to rise more rapidly than when serum was not injected. (See Table II, page 82.)

After the removal of the thyroid gland from rabbits, their gas exchange is first decreased, but after a few weeks it returns to its former level. If the thymus is then removed, the gas exchange falls very rapidly and remains subnormal until the death of the animal. Asher and Ruchti concluded from this that the thymus may assume a compensatory function when the thyroid is absent or functioning imperfectly. To the spleen, these workers assign a function antagonistic to that of the thyroid, because after splenectomy they obtained a marked increase in the carbon dioxide output which sank again to a level below normal after the thyroid had also been removed.

In myxoedema subjects the exchange of gases is very much lowered, but it is possible to restore the gas exchange and to maintain it at a normal level for periods of about ten days with a single 20 milligramme dose of thyroxin, the hormone isolated by Kendall from the thyroid gland (Plummer).

TABLE II.

INFLUENCE OF INTERNAL SECRETIONS ON GAS METABOLISM.

No.		Gland	Operation or Disease	Grams per kilo and hour O_2	CO_2	Observer	Remarks
1	Man		Normal	0.33	0.31	Magnus-Levy & Falk	Reck'd in ccm.
2	"	Thyroid	Basedow	0.59	0.69	Magnus-Levy	"
3	"	"	Sporadic Cretinism	0.25	0.25	" "	"
4	"	Hypophysis	Tumor	0.25	0.27	Bernstein	"
5	Dog		Normal	0.61	..	Loewy & Richter	"
6	"	Testes	Castration	0.52	..	" "	"
7	"		Normal	0.57	0.53	Slowtzoff	"
8	"	Hypophysis	Removal	0.40	0.38	Aschner & Porges	"
9	Rabbit		Normal	1.61	1.35	Labbé & Stévenin	"
10	"	Thyroid	Removal	1.27	1.10	" "	"
11	"	Parathyroid	Removal	1.62	1.44	" "	"
12	"	Thyroid	Feeding	1.84	1.64	" "	"
13	"	Thymus	Removal	..	1.25 [1]	Asher & Ruchti	"
14	"	Testes	Removal	..	1.19 [2]	Asher & Bertschi	"

[1] Average of three experiments.
[2] From the 11th to the 20th day after operation. Before operation 1.28 g.

Adrenalin injections do not increase bodily heat by direct stimulation of oxidation processes within cells but indirectly through a constriction of the cutaneous blood vessels; this forces the blood into the great vessels of the interior, thus diminishing heat loss and causing a rise in body temperature even though heat production remains unchanged.

The influence of the germ glands on heat regulation is shown in the different temperatures of the two sexes. In new-born boys the rectal temperature is about 0.33° C. higher than in girls; the heat production per square meter of surface and per day is estimated for boys from the seventh to the tenth year at 1,440 calories; for girls at 1,390 calories. From puberty to about the 18th year it is 1,200 calories for boys and 930 for girls (Vierordt). The average heat production per hour and kilogram of body weight was for 89 adult men, 1.07; for women 1.05 calories (Benedict). Temperature differences are found in the two sexes of lower animals; the drake was found by one observer to have a temperature of 41.9°, the duck, 42.2°C.; in female rats the temperature is said to be 0.5° higher than in the male. In the guinea pig the difference reaches 0.6° to 0.7°. In castrated female guinea pigs the temperature is lowered about 0.4°, but in castrated males no such differences are observed. In feminized male animals the temperature rises to that of the normal female, but in the masculinized female it does not show any changes (compare Chapter VII, 6, Lipschütz).

On the other hand, the *external* temperature may also

affect the activities of the glands of internal secretion. Adler found that in cultures of frogs' larvæ kept in hot surroundings their thyroids from the very beginning were smaller than the thyroids of frogs kept at ordinary temperatures, and that by a gradual rearrangement of the single follicles the organs even diminished in size as the animal grew larger. But when these frogs were placed in a room with lower temperature the follicular epithelium began to regenerate and the colloid to liquify, with the result that the whole gland again grew larger.

In short, the influence upon heat production of the glands with internal secretions may be summed up as follows: The thyroid and hypophysis increase the production of heat chemically, by augmenting oxidation processes within the cells of the body; the adrenals increase the body heat, but only through a mechanical adjustment which serves to decrease the loss of heat from the skin; this adjustment is brought about by an increased production of adrenalin.

2. *Proteins, Fats and Carbohydrates*

(a) *Proteins:* One of the longest known functions of the thyroid is its regulation of protein metabolism After removal of this gland the nitrogen excretion sinks, on an unchanged diet, to about one-half what it was before, so that in subjects in whom a negative nitrogen balance had existed, protein retention may be obtained after operation. In cases of thyroid hypofunction, such as myxoedema, a lowering of the nitrogen metabolism by about 50 per cent has been observed. If thyroidless ani-

mals are fed with fresh or dried thyroid gland, or given injections of its watery extracts, their lowered nitrogen output rises again; the same change takes place in myxoedema patients given thyroid products. In normal ani-

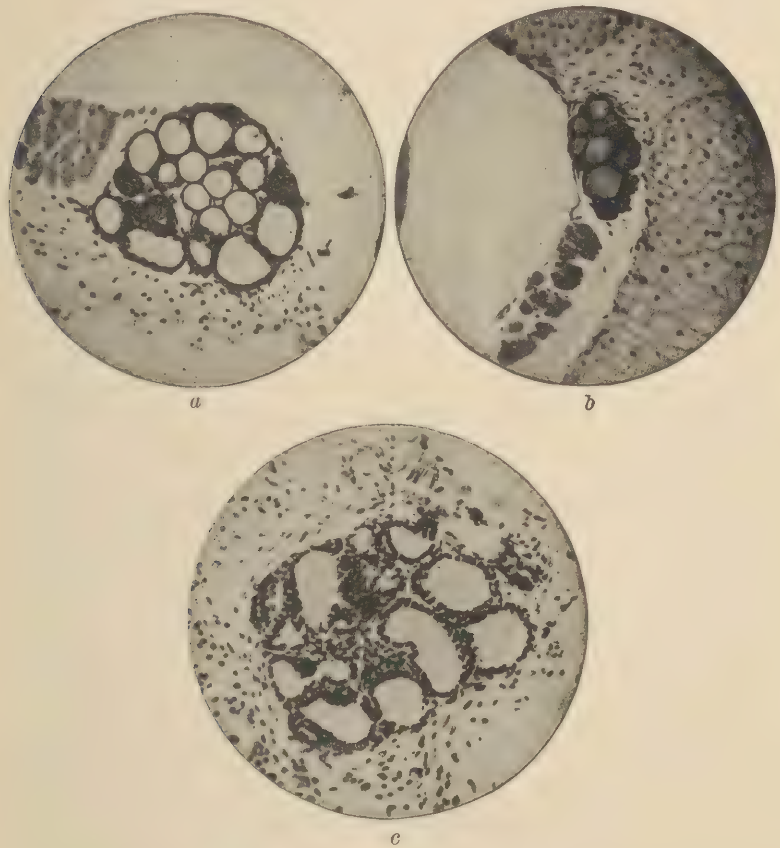


FIG. 15. After Adler (about $\times$ 85).

a. Frontal section through the thyroid of a normal 30-day larva of Rana temporaria. Temperature 18° C.

b. Thyroid of a 50-day larva bred at 28° C.

c. Thyroid of a 68-day larva kept at 31.5° C. for 18 days, then for 50 days at 10° C.

mals thyroid gland dosage does not always increase the nitrogen output. An example showing the relationship of the thyroid to protein metabolism is given in the following table taken from Voit, which gives the nitrogen metabolism determinations for an adult male dog.

TABLE III.

NITROGEN OUTPUT AFTER THYROID FEEDING.

	N-intake	N-output	N-difference	CO_2 Output in grams per day
Preliminary period.......	20.61 g	19.08 g	+1.63 g	330
During and after feeding	20.86 g	21.21 g	—0.35 g	382

The figures of the first row show the normal daily averages during a four-day preliminary period in which 20.61 grams of nitrogen in the form of meat was fed to the animal; in addition to this a rich supply of fats and carbohydrates was also given. Then follows a four-day period, in which 10 grams of fresh thyroid gland was added daily to the same diet; and, finally, a last four-day period, when the diet of the first four days was again resumed but without the thyroid feeding. The figures of the second row give the combined averages for the last two periods.

When in cases of increased function of the thyroid, as in Basedow's disease, a nitrogen-free diet with abundant fat and carbohydrate is given, the nitrogen output may reach a daily total of 8 grams, whereas in normal persons it is only about 4 to 5 grams. The Basedow patient

needs, therefore, to take in much more nitrogen in his food than the ordinary person, for his output is greater; his nitrogen equilibrium would otherwise not be maintained and he would suffer loss of his own tissue protein. It seems, however, that this greater destruction of protein material is not the only cause underlying the demand for extra food, but that this is made even more urgent because of the accelerated destruction of fats and carbohydrates. This is caused by increased oxidation, a condition similar to that described by Eckstein and Grafe as *luxus consumption* of food. These investigators found that an overabundant diet, but with protein in quantities even slightly below the minimal body requirement, caused a daily increasing rise in the rate of metabolism. But when they extirpated the thyroid the fasting nitrogen requirement fell 20 percent; on the same diets the body weight increased, and there was no more *luxus consumption.* From this they concluded that the active incretion of the thyroid must play a most important part in this very striking increase in the rate of metabolism during overnourishment. Into this circle of facts also fits the observation that if Basedow patients are given thyroid gland substances it is possible to reduce their negative nitrogen balance by providing an abundance of carbohydrates and fats in their diet; this is further proof that the action of the thyroid secretion consists in a stimulation of cell metabolism, which is not limited solely to a greater breaking down of proteins. This conception is opposed to old observations made by Voit and Magnus-Levy; they found that animals fed on thyroid

substance showed, even with an abundant fat supply, a persistently higher nitrogen output than the controls. But we may agree with Falta that the diet in these cases was very unbalanced and its carbohydrates insufficient. Falta also points with reason to the investigations of Rudinger, who succeeded in reducing the nitrogen output to a normal minimum in animals fed with thyroid when these were furnished with large amounts of carbohydrate. Thyreoglobulin and thyreoglandol, two preparations obtained from the thyroid, also increase nitrogen excretion in fasting animals, in thyroidectomized as well as in normal animals.

The following tables show figures obtained by Abelin:

1. Nitrogen output of a normal animal during eight fasting days; reduction of weight from 24.65 kilos to 22.50 kilos; for five days, from the 3rd to the 8th, daily injections of 16.5 cubic centimeters of thyroglandol; increase in nitrogen excretion, 50 percent.

Day	1	2	3	4	5	6	7	8
G.N.	3.06	2.10	2.30	3.25	2.79	5.52	4.30	3.96
G.N. pro Kg. body weight........	0.125	0.088	0.097	0.138	0.119	0.242	0.189	0.176

2. Nitrogen excretion of a thyroidless animal during 8 fasting days; from the 5th to the 8th day, 20 cubic centimeters thyreoglandol injection daily; reduction of body weight from 24.45 to 22.4 kilos; increase in nitrogen excretion about 40 percent.

Day	1	2	3	4	5	6	7	8
G.N. per Kg. body weight........	0.140	0.060	0.140	0.164	0.172	0.180	0.156	0.201

In other series of experiments thyroidless dogs reacted more strongly to the administration of dried thyroid than did normal dogs, the increase in nitrogen elimination having been 137 percent in the former against 124 to 128 percent in the latter. This phenomenon is often observed in the treatment of myxoedema.

Similar effects have been obtained with phenylethylamin and paraoxyphenylethylamin (proteinogenus amins which may be obtained from the amino acids phenylalanin and tyrosin), and from this the conclusion has been drawn that perhaps the thyroid incretion may be of an amino character (see Chapter XI). Daily injections of about 1.5 milligrams of various amins caused the nitrogen output, which had previously been 0.09 grams per kilo of body weight, to rise to 0.414 grams during the injections, and in the subsequent period to remain for a long time at 0.6 grams (Abelin).

In the older works experimental results contradictory to those obtained in recent times are often recorded—increased and not decreased nitrogen excretion in dogs after thyroid removal, and a simultaneous appearance of symptoms which we now know to be due to the absence of the parathyroids, namely, tetany. The latter accident may be ascribed to the circumstance that at that time the identity of the parathyroids as specific organs was not recognized, and that, being unwittingly removed with the thyroid gland, their loss was followed by tetany symptoms. Hunter has recently recalled the fact that increased nitrogen was found in the urine of thyroidectomized sheep only when the parathyroids had also been removed; re-

moval of the thyroid alone always produces a fall in the nitrogen output.

The nature of the nitrogen compounds excreted in the urine appears to indicate that it is not the physiological nitrogen exchange that is increased, but that the excess nitrogen excretion is the result of severe injury to the protein metabolism processes; ammonia nitrogen is increased at the expense of urea; the same is true of the creatin and polypeptid fractions. Bases which are not normal constituents of the urine are also excreted, for example, histamin and paraoxyphenylethylamin (derivatives of the amino acids histidin and tyrosin). We may ascribe the increased nitrogen excretion occurring in tetany to an increase of amino compounds in the blood, for, intravenous injections of various proteinogenous amins are, as we have already seen, followed by an increased nitrogen output. By injecting parathyroid extract in "parathyroid dysfunctions," Norvig succeeded in bringing the dysregulation of the ammonia nitrogen fraction and the hydrogen ion concentration back to normal. This striking derangement in the metabolism of intermediate protein substances, raises the question whether the subsequent breaking down of amino compounds occurs normally in the parathyroids or in the liver? If this occurs in the parathyroids, then a detoxicating function must be ascribed to them. This view, if true, would add support to that theory, according to which only antitoxic functions were ascribed to the endocrine glands. But if the breaking down of amins takes place in the liver, then we must assume the production

in the parathyroid of a hormone which, like a specific ferment, activates the liver cells to such action. The fact that animals suffering from tetany have, in addition, a tolerance for carbohydrates greater than is normal, points also to a general disturbance which, according to the latest observations, appears to have some connection with guanidin metabolism.

The suprarenals seem to exercise but little influence upon protein metabolism; neither the injection of adrenalin nor the removal of the glands affects the nitrogen output of the organism. Adrenalin injections, however, increase the excretion of creatinine, methyl-guanidin-acetic acid, the anhydride of creatin (Roux and Taillandier); perhaps this is due to increased wear of muscle substance produced by the increased action of the added hormone. This interpretation is in harmony with the theory, that creatinine is a typical product of muscle cell metabolism. In injuries to the adrenals and in Addison's disease the urinary creatinine excretion is diminished.

Extracts of the posterior lobe of the pituitary body, which, like adrenalin, directly stimulate smooth muscle activity, produce also, like adrenalin, an increase in nitrogen excretion.

Removal of the pancreas increases the urinary nitrogen in a fasting animal three to four times (Falta and his co-workers). But it is very doubtful whether it is permissible to attribute this increase to the loss of the specific incretion of the pancreas; it is far more likely that, in order to meet the energy needs of the body caused by the

disturbance in fat resorption and by injury to carbohydrate metabolism, the organism is forced to an increased protein utilization and decomposition, resulting in increased nitrogen excretion.

Castration is without influence on protein metabolism. The increased capacity for work and the hypertrophy of muscle substance which have been described as a sequence of testicular extract injections are doubtless due to ordinary hypertrophy following increased muscular activity, and are not the result of an increased cell protein production brought about by the injected testicular hormone.

Summing up the effect which the internal secretions have upon nitrogen exchange, it may be said that the thyroid, by causing an acceleration in the total cell metabolism, stimulates the body to increased protein decomposition; but that the increased energy need may be satisfied by a more plentiful diet of fats and carbohydrates. The parathyroids control the cleavage of intermediate protein products, probably by means of a hormone which activates the liver cells. The adrenals and the hypophysis further the breaking down of smooth muscle protoplasm, and thereby increase the excretion of creatinine.

(b) *Fats:* With respect to protein metabolism, determinations of the nitrogen balance always give us a certain measure of information concerning intracellular processes, but we are without any equally exact method for measuring fat metabolism. Here we are still principally dependent upon the study of the body weight and the behavior of the fatty tissue deposits in the subcutaneous tissues. And when it becomes necessary to

determine whether fat absorption and assimiliation is taking a normal direction we are compelled to depend upon rather uncertain expedients, such as the determination of basal metabolism and the measurement of the respiratory quotient. The problem of fat metabolism is made still more difficult by the fact that carbohydrates may be converted into fats and that diets rich in carbohydrates may produce corpulency; also, in the temperate zones, increased food intake is usually equalized by increased muscular activity whereby fat accumulation is naturally prevented.

Clinicians have described the most varied disturbances of fat metabolism in connection with diseases and dysfunctions of the endocrine glands, but without always being successful in furnishing proof as to whether the changes in the glands were the consequences of these fat metabolism disturbances or their causes. The commonest cases of fat storage are those occurring in thyroid insufficiency or after thyroid removal. As we have already seen there is, in such cases, a marked fall in basal metabolism with a reduction of oxidation processes amounting to one-half or more, so that when the food intake remains quantitatively the same, the fats and carbohydrates are no longer fully utilized as in normal persons, but are deposited in the storage depots, in the liver as glocogen, and in the subcutaneous tissues as fat accumulations. The administration of thyroid preparations in these thyreogenous forms of adiposity is followed by a quick disappearance of the accumulated fat, thus proving that the cause of this fat accumulation is a

diminished combustion of intermediary metabolism products due to a lack of thyroid hormone.

The obesity which follows removal of the gonads cannot be explained in so unequivocal a manner. Castration of domestic mammals was already done for economic reasons in pre-Christian times, as it was known that their fattening could thus be accomplished with smaller amounts of food. Castrated animals become more sedate; the fiery disposition of the stallion and bull give way to the phlegmatic tendencies of the gelding and ox. In human beings, germ glands were often excised to prepare the subjects for becoming asexual harem watchmen or soprano singers. This eunuch type also shows marked fat accumulations, especially in the region of the breasts and at the sides of the hips. This type of fat deposition is typical for castrates since in obsity due to excess feeding the chief storage region is the connective tissue of the abdomen. In eunuchs, in addition to the places already mentioned, the fat also markedly invades the muscle tissues; the muscles then degenerate and in consequence the eunuch is conspicuous for his sluggish and lazy movements. This brings up the question whether this exogenous circumstance, lack of muscular activity, causes the diminished combustion and increased accumulation of fat in the eunuch, or whether endogenous conditions produce a lowered basal metabolism and cause the obesity. This question has not yet been finally settled, but it seems as if both factors operate in producing this condition. One thing is certain: the changed distribution of the fatty tissue is due to the loss of function

of the germ glands. This was exemplified in many cases during the late war where soldiers had their testicles removed because of irreparable injury; all showed, after a time, the typical eunuch fat distribution, but when they were afterwards implanted with healthy human testicles they recovered their former outlines. Dwarfing of the incretory portion of the testicle in eunuchoidism causes essentially the same fat deposition. On the other hand, in cases where the generative portion of the testicles is partially lost, but the interstitial part is retained, as in cases of cryptorchism, a normal masculine shape without abnormal fat deposition is the rule.

Atrophy of the testicles may also occur as a sequence to diseases of the hypophysis, caused usually by an adenoma of the anterior lobe (Berblinger). Tumors of the posterior lobe produce another definite syndrome, dystrophia-adiposo-genitalis, in which in addition to the lack of the secondary sexual characters the most striking superficial symptom is the deposition of fat at the hips, pubes and mammæ, resembling the fat distribution in the eunuch. There is also in these cases a simultaneous decrease in the basal metabolism. But these symptoms, according to Falta, are due to a deficiency of the interstitial glands and not of the hypophysis; neither the eunuchoid fat deposition nor the lowered basal metabolism, he thinks, is due primarily to a disturbance of the hypophyseal incretion. Other hypotheses connect these changes not with the hypophysis hormone but with the irritation of a center lying in the floor of the thalamus, an irritation caused by pressure of the growing hypo-

a *b*

Fig. 16. *a.* Eunuchoid 25 years of age, showing great fat accumulations in the mammary and hip regions (Falta). *b.* Dystrophia due to tumor of hypophysis in a 16-year-old subject. Fat accumulations on the breasts, hips, outer surface of thighs and mons veneris (O. Hirsch).

physeal tumor (Erdheim and Aschner). But the fact that these symptoms appear after removal of, or mechanical injury to the hypophysis, and that they are ameliorated by hypophysin and by thyroid extract, points to the likelihood that an incretory disturbance *is* involved.

The pancreas also plays a large part in fat metabolism. Its external secretion, the pancreatic juice, by means of its lipases—fat-spliting enzymes—reduces the fats to fatty acids and glycerine, both of which are later absorbed from the intestine. In addition, the pancreas incretion brings about a saving of fat by stimulating carbohydrate metabolism. (See next chapter.) Only when there is a great scarcity of sugar do the cells attack the fat for energy production, whereas during abundant carbohydrate feeding the reverse occurs; not only is the fat then spared but the superfluous carbohydrate material is converted into fat and deposited as such. But it seems that in addition to this indirect action on fat metabolism the pancreas has also a direct influence upon fat combustion; this may be conceived as follows: The fatty acids of higher molecular weight, through the gradual, oxidative cleavage of the separate hydrocarbon groups, are first converted by the liver cells into lower fatty acids and, then, through butyric acid, oxybutyric and acetoacetic acid into acetone. The last three decomposition products are finally oxidized in other body cells through the agency of the pancreatic hormone, forming the end products, carbon dioxide and water. The pancreatic hormone thus takes an active part in fat metabolism.

CH_3	CH_3	CH_3	CH_3	CH_3	+ Pancreas extract
$(CH_2)x$	CH_2	CHOH	CO ——>	CO	
——>	+O	+O			$+4O_2$
CH_2	CH_2	CH_2	CH_2	CH_3	
	——>	$-H_2O$	$-CO_2$		$=3CO_2+3H_2O$
COOH	COOH	COOH	COOH		
Fatty acid (Stearic)	Butyric acid	B—Oxybutyric acid	Aceto acetic acid	Acetone	

These assumptions are supported by the following data: It is possible by passing fatty acids through a surviving liver to produce acetone. After removal of the pancreas the acetone bodies—oxybutyric acid, aceto-acetic acid and acetone—are not oxidized into their final products, but appear in the urine in large quantities; their excretion may, at the same time, be increased through feeding with butyric acid, caproic acid and fats, or it may be diminished by carbohydrate feeding, the carbohydrates, according to our conception, being split up by the cells of the organism in place of the fatty acids. Since in depancreatized animals the liver has lost its capacity for storing glucose as glycogen, the non-stored glucose is retained in the blood and being unutilizable is at once eliminated from the blood by way of the urine. Hence, if it is desired to prevent acetone excretion, the supply of carbohydrate must not be long interrupted.

At this place it may also be well to recall those theories, which likewise ascribe to a hormone, secretin, presumably

formed in the mucosa of the small intestines, the power of stimulating the secretion of pancreatic juice. By means of an 0.4 percent solution of hydrochloric acid, or of a 1 per cent solution of common salt, it is possible to isolate from the intestinal mucosa a substance which, when injected subcutaneously, will rapidly increase the flow of pancreatic juice. In dogs, a flow of about 8.5 cubic centimeters per minute may be thus obtained. If two dogs are joined together by means of an anastomosis between the carotid artery of the one and the jugular vein of the other, then injections of secretin into the one dog is followed immediately by a flow of pancreatic juice in the other; this furnishes proof of the true hormone nature of the injected substance. The normal stimulus for the production of the intestinal incretion is the outflow of hydrochloric acid from the stomach into the duodenum; the pancreas may also be artificially stimulated to an increased production of pancreatic juice by injecting hydrochloric acid into the duodenum or even into an isolated loop of intestine whose nervous connection has been severed from the rest of the body (Baylis and Starling). From this it may be seen that we must abandon the earlier explanation of Pawlow which ascribed the inauguration of pancreatic secretion to a nervous reflex caused by intra-intestinal pressure on Auerbach's plexus.

Fat accumulation has also been ascribed to diseases of the pineal gland. This gland, as will be shown later, retards the development of the germ glands; this fact

gave rise to the hypothesis that in hyperfunctioning of the pineal body disturbances in fat metabolism occur indirectly through the accompanying atrophy of interstitial tissue in the germ glands.

In connection with fat metabolism it may also be mentioned that a special rôle has been ascribed to the suprarenal cortex in the metabolism of lipoids, particularly of cholesterin. The great accumulation of cholesterol in the cortex of the suprarenals has suggested that these organs may be a storage place for this substance, and that from there the lipoid bodies may be distributed through the organism (Landan). Other hypotheses go further and are inclined to allot to the suprarenal cortex a hormonic influence upon the lipoid metabolism in other organs. Further investigations may or may not substantiate these assumptions; at present the only evidence is based upon the increase of lipoids in pregnancy.

The sum of our present knowledge in regard to the regulation of fat metabolism by the internal secretions is as follows: Hypofunctioning of the thyroid or of the hypophysis or of the germ glands decreases oxidation processes, thus diminishing the normal combustion of fat and favoring its accumulation; the internal secretion of the pancreas brings about the complete oxidation into acetone bodies of the split-up fatty acids; it enables the organism to store sugar as glycogen, thus saving the fats from being used for energy, and, with abundant nourishment, favoring fat accumulation. The cleavage of fat in the intestine is promoted through a hormone action of the incretion of the intestinal mucosa, which, through stimu-

lation of the pancreas, increases the secretion of pancreatic juice.

(c) *Carbohydrates:* In the previous chapter we pointed out the importance of the pancreas for the metabolism of carbohydrates. We also called attention to the fact that removal of this organ causes an increase in the blood sugar, with a simultaneous decrease of liver glycogen and the production of glycosuria. (von Mehring and Minkowski.)

If the surviving heart from a depancreatized dog is transfused with the dog's own blood to which glucose has previously been added, the glucose does not gradually disappear from the blood as would happen were the heart from a normal dog; only after the addition of pancreatic juice to the perfused blood does the heart muscle regain its capacity to store dextrose and to utilize it as a source of energy (Starling). We must, therefore, ascribe to the pancreatic incretion assimilatory qualities which promote glycogen synthesis. Since the blood sugar level in a normal organism varies extremely little, at most only about one-tenth of one percent, the reconversion of glycogen into glucose must in some way be so regulated as to maintain this nearly constant percentage. This must evidently be accomplished either through nervous or incretory control of the liver cells, which, in fact, normally retain the total quantity of sugar delivered from the intestines through the portal vein.

The very complicated processes in carbohydrate metabolism have been gradually classified in recent years, so that it is now possible for us to form an approximately

clear idea of the part which the separate endocrine organs take in it. An historical retrospect of the investigations concerning this subject may help in its understanding. In the year 1850 Claude Bernard was able to prove by his well-known "piqûre" experiment, that after injury of the floor of the fourth ventricle dextrose appears in the urine, and that, at the same time, hyperglycemia with loss of liver glycogen occurs. He thus obtained the same phenomena with which we are now familiar in pancreas extirpation. After section of both splanchnic nerves the puncture had no effect upon sugar excretion. In accordance with the theory of *nervous correlation,* these results were held to show that glycogen decomposition was normally regulated by nerve stimuli. But Blum (1901) was able to show later that injections of adrenalin also produce hyperglycemia and glycosuria. These findings were confirmed again and again; by the injection of 1 milligram of adrenalin a rapid rise of blood sugar was obtained, reaching 0.7 percent within 2 to 3 hours and returning to normal only after 7 to 9 hours; adrenalin injections produced glycosuria even when the liver had previously been made glycogen free by strychnine injections, and when only muscle glycogen remained as the source of sugar in the urine.

When the older observers found that glycosuria no longer occurred after the suprarenals had been removed, or their nerve supply severed, they assumed that the sugar puncture stimulated the adrenals to increased adrenalin production, and thereby promoted a greater glycogen decomposition in the liver, thus causing glyco-

suria. But they had neglected to determine the sugar content of the blood. Freund and Marchand, who did this, found that even after the removal of the suprarenals the puncture resulted in hyperglycemia, although the hyperglycemia was less acute than that obtained in animals with intact suprarenals. Naturally, hyperglycemia occurred only when the liver contained glycogen. From these results Freund and Marchand concluded that the permeability of the kidneys for sugar is increased through the influence of adrenalin.

We already saw in an earlier chapter, that the blood vessels of the kidney are constricted by injections of adrenalin, while injections of hypophysin dilate them; this antagonism between the suprarenals and the hypophysis is manifested also in carbohydrate metabolism; injections of pituitrin prevent the glycosuria which follows adrenalin injections, though it does not check the hyperglycemia produced by the latter. The same results are obtained also by feeding with dried hypophysis. In diabetics the pituitary gland is reduced in size and becomes permeated with atrophic foci; the number of its œsinophile cells is also diminished (Kraus).

After removal of the thyroid, the glycosuria which follows adrenalin injections is of a much lesser degree, but feeding with thyroid extract increases glycosuria and reduces the glycogen content of the liver from 4 percent of the organ's weight to but 0.1 percent. In explanation of this, it was formerly assumed that the thyroid hormone directly stimulates the suprarenal to an increased adrenalin production, but later observations, such as

enlargement of the hypophysis after thyroidectomy, point rather to an inhibitory influence of the thyroid upon the incretion of the hypophysis, with a consequent reduction in its antagonism to adrenalin. Trendelenburg is inclined to deny altogether the coöperation of adrenalin in the events following sugar puncture. He found that after diabetic puncture the quantity of adrenalin capable of producing still more glycosuria (0.002 mg. per kg. of body weight per minute) always induces, in addition, an increase in blood pressure; but in rabbits narcotized with urethan, no such rise in pressure is produced by puncture. On the other hand, it has been shown that after puncture there is in the adrenal vein a greatly increased quantity of adrenalin, and Kahn and also Fujii report that after section of one splanchnic nerve the chromaffine granules of only the intact side disappear after diabetic puncture, and that for a long time after the operation the affinity of the abdominal paraganglia for chromium is diminished. This they regard as evidence of adrenalin exhaustion. Jarisch, however, denies that these results take place. Finally, it is stated that after repeated injections of adrenalin the experimented animals no longer react with glycosuria, but that diabetic puncture still causes a rise in blood sugar (Biberfeld).

How, then, can we bring all these partially contradictory findings into harmony with one another and obtain a unified conception of the relationship between diabetic puncture, the suprarenal glands and glycogen-dextrose transformation? It has been pointed out that the results produced by the use of large pharmacologic doses of

adrenalin cannot be compared with the effects due to its very meager normal concentration in the blood, and that its physiological function is not to act as a direct excitant and stimulus producer, but only as a means by which to make the endings of the sympathetic nerve more receptive to stimuli. The central irritation produced by injury to the fourth ventricle stimulates the liver cells to greater glycogen transformation (electrical stimulation of the peripheral stump of the sympathetic has the same effect); at the same time the suprarenals also are stimulated to increased secretion by way of the sympathetic (a phenomenon also produced by stimulation of the splanchnic). This increased adrenalin production results in a still greater irritability of the sympathetic nerve endings in the liver, and thereby their receptivity to the mechanical irritation produced by puncture becomes even greater, and the glycemia reaches a greater height than it would were the adrenals excluded by removal or by section of their nerves. Furthermore, the greater irritability of the sympathetic nerve caused by increased adrenalin production also involves the nerve endings in the kidney, and causes that organ to become more permeable for sugar, just as injections of phloridzin cause a greater permeability of the kidney for dextrose so that glycosuria occurs, even though the blood sugar values remain normal. According to this conception, the contention of Trendelenburg and Fleischhauer that adrenalin possesses no hormonic action loses its foundation. Indeed, after diabetic puncture a very small increase in the adrenal incretion—less than enough to bring adrenalin concentra-

tion to a point which will raise blood pressure—suffices to increase immensely the irritability of the liver cells to splanchnic stimulation, whereas a glycosuria produced by a single adrenalin injection requires a relatively great dose.

There remains still to explain the connection between the pancreas and the adrenals in their relation to carbohydrate metabolism. If, after opening the abdominal cavity, the pancreas of a living rabbit be painted with a diluted adrenalin solution, dextrose very soon appears in the urine. Adrenalin, therefore, depresses the action of the pancreatic hormone, which normally promotes glycogen synthesis in the liver and muscle cells, and, in this case, the continuous nerve stimulation which normally maintains the sugar equilibrium through glycogen splitting goes on at a greater rate than glycogen synthesis and permits sugar to appear in the urine.

The carbohydrate metabolism after diabetic puncture is schematically represented in the diagram on the following page.

If in this schematic representation we remove the pancreas and with the pancreas its retarding effect upon the flow of sugar into the blood, we will obtain a true picture of pancreatic diabetes or diabetes mellitus, a disturbance which is recognized to-day as due to an insufficiency of the internal secretion of the pancreas with a synchronous over-irritability of the chromaffine system. Absence of the suprarenal function explains the low blood sugar content in Addison's disease, a condition caused by the complete or partial destruction of the

chromaffine substance. The relation of the hypophysis to carbohydrate metabolism, as exemplified in this schema, requires this additional explanation: the statement previously made, according to which pituitrin retards the sugar mobilization produced by adrenalin

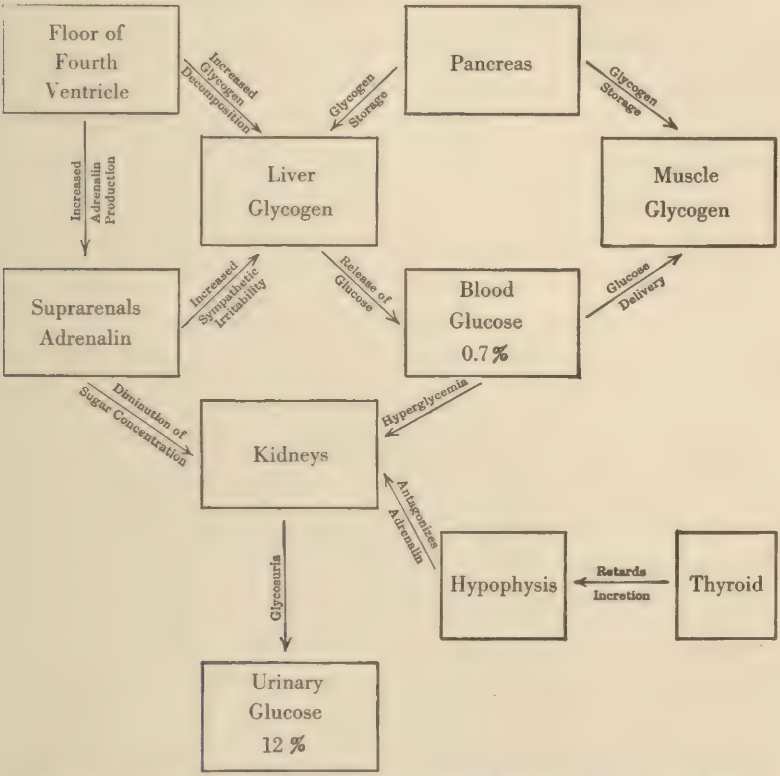


FIG. 17. Schematic Representation of the Relations Between Sugar Puncture and the Internal Secretions.

injections, is contradictory to the work of Cushing, who found that intravenous injections of posterior lobe extracts always had just the opposite effect and led to

glycosuria. But Falta, Bernstein and Priestley could never obtain these results; neither were they ever able to produce a decrease in the carbohydrate tolerance—alimentary glycosuria—by feeding with large amounts of dextrose. Other investigators have also contradicted the statements of Cushing. It is also true that the glycosuria which has been observed after loss of function of the hypophysis, as, for instance, the glycosuria which accompanies dystrophia-adiposo-genitalis, does not fit into his theory; it can, however, be explained in accordance with our schematic representation as due to loss of the hypophysis and consequent overbalancing of adrenalin action.

Lesser has proposed the hypothesis that in the liver the glycogen splitting ferment, diastase, and the glycogen itself are separated from one another, and that this separation may be terminated either by adrenalin or by the extirpation of the pancreas. After pancreatectomy, sugar introduced with the food can no longer prevent the combustion of body fat, and the two substances cease to be interchangeable heat producers. It remains to be seen whether these newer conceptions, which attribute chief importance to fermentative processes of the internal secretions as factors which influence sugar metabolism will replace the older indefinite views of nervous or chemical stimulation of cells. Héden believes that it is the function of the Langerhans island cells to produce a co-ferment which activates not only the glycogen forming ferment of the liver, but also its fat and protein splitting enzymes as well.

3. *Inorganic Compounds*

As we have seen, one main incretory function of the pancreas consists in the transformation of dextrose ($C_6\ H_{12}\ O_6$), which crystallizes and forms true solutions, into the amorphous polysaccharide, glycogen $(C_6\ H_{10}\ O_5)x$ which forms only a colloid solution with water and does not diffuse through animal membranes—a transformation that is produced by a splitting off of water and a polymerization of the sugar molecule. This transformation makes it possible for the body to store within the cells its most important energy producer, dextrose, and not merely to store the dextrose which is conveyed to the liver in the portal circulation, but also that which is produced from fats and amino acids in the intermediary cell metabolism. Such a sugar storage is, indeed, an indispensable factor in our complex metabolism.

Analogous to this sugar storage is the storage of the body's inorganic substances which must all be anchored and be made non-diffusible to prevent their too sudden inundation of the cell contents with a consequent serious disturbance of vital processes.

Calcium plays a great rôle in the building of all the tissues. In the form of its carbonates and phosphates calcium takes part in the formation of bone and it is calcium deposition that transforms the soft, elastic cartilage into the hard, unyielding spongiosa. As these two calcium salts are feebly soluble in water, and as, in the bone, they are, besides, imbedded in a gelatinous medium, they diffuse out of this medium only with great difficulty.

Gassman believes that in bone calcium phosphate occurs in the form of a complex polymeric salt, having undergone a transformation analogous to that by which soluble dextrose is polymerized to insoluble glycogen.

$$\left[\mathrm{Ca}\left(\begin{matrix}\mathrm{OPO_3.Ca}\\ \gt\mathrm{.Ca}\\ \mathrm{OPO_3.Ca}\end{matrix}\right)3\right]\mathrm{CO_3} + x\mathrm{H_2O}.$$

Calcium also plays an important rôle in modifying the irritability of the nervous system; calcium salts depress nerve irritability, while all salts that precipitate calcium, increase it. For instance, an induction current which is just strong enough to cause a contraction in the frog's muscle-nerve preparation may be much reduced and still produce a response if the preparation is treated with diluted oxalic acid to precipitate its calcium salts. If dog's blood is dialyzed against a calcium-free solution, and is then used to perfuse the isolated limb of a living animal, the response of the perfused limb to a galvanic current will be much greater than that of the other limb. For the same reason, muscle preparations kept in calcium-free Ringer solutions acquire an increased irritability because of the diffusing out of their calcium salts, whereas if they are kept in Ringer solutions containing calcium such muscles retain their normal irritability for 24 hours.

If blood serum of parathyroidectomized cats is used to perfuse a beating frog's heart the contractions are diminished and resemble those obtained when the perfusion fluid is a Ringer solution deficient in calcium. The ash of such a serum, dissolved to form a solution

isotonic for the frog's heart, produces the same effect as the whole serum. (Trendelenburg.) These examples may bring us nearer to an understanding of the manifestations occurring in the tetany which is produced by extirpation of the parathyroid glands. In parathyroidless animals an over-irritability of the sensory and motor nerves exists; mechanical or psychic stimulation brings about the most violent muscular cramps, especially in the region of the upper extremities. The threshold of stimulation of the ulnar nerve in man is normally about 0.9 milliamperes for the anode make shock and from 2.5 to 3 milliamperes for the cathode break shock. In cases of tetany these values sink to 0.1 milliamperes for the make shock and sometimes still lower for the break shock. Comparison of the total ash of normal animals and of those which had suffered from tetany show a calcium deficiency in the latter; in these the blood is also found to be greatly impoverished in calcium.

Metabolism investigations of parathyroidless animals always show a negative calcium balance, with a simultaneous increase in the excretion of inorganic phosphates and magnesium compounds in the urine and feces. Subcutaneous injections of calcium or magnesium salts in parathyroidless animals decrease the heightened nervous irritability, so that the convulsions cease. Lanthanum and thorium compounds also have the same effect. The bones of parathyroidless animals are softer and more brittle than those of their controls; after artificial fracture, which is much easier to produce in such animals than in healthy ones, callus formation is abnormally slow

or altogether absent; chemical examination of the callus also demonstrates its calcium poverty.

The calcium impoverishment in parathyroidless animals is also responsible for the simultaneous disturbance in the growth of teeth. In rabbits, within six to ten

FIG. 18A. Cross-section through the lower incisor of a normal rat. *S.e.*, enamel epithelium; *Sch.*, enamel; *vk*, calcified dentine; *uk*, uncalcified dentine; *P.*, pulp. (Fleischmann.)

weeks after parathyroid removal, there appear on the anterior surface of the canine teeth white milky spots, which, as growth continues, gradually come nearer to the tip of the teeth. These spots show areas of meagre

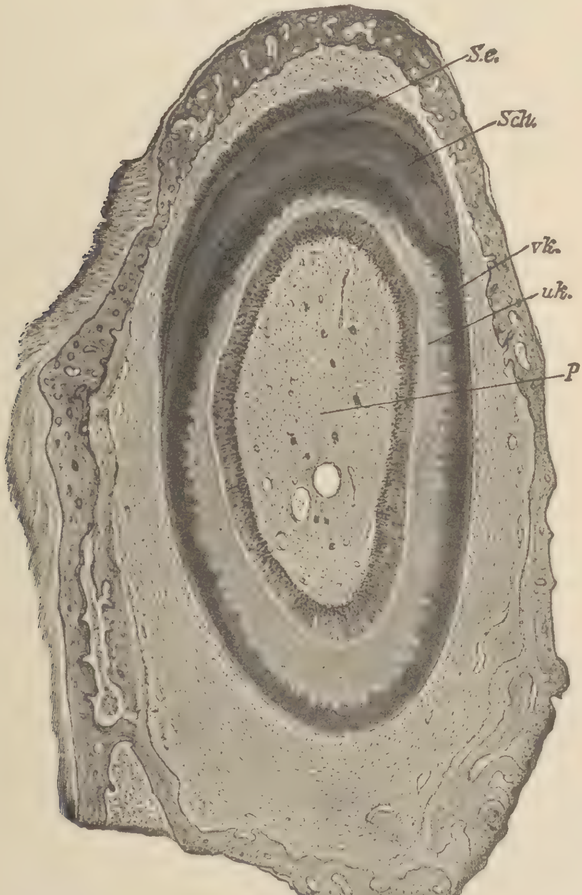


Fig. 18B. Cross-section through the lower incisor of a parathyroidless rat. *S.e.*, enamel epithelium; *Sch.*, enamel; *vk.*, calcified dentine; *uk.*, uncalcified dentine; *P.*, pulp. (Fleischmann.)

calcification of dentine and an absence of enamel. Such teeth break easily, and destructive ulcers soon appear on the fracture surfaces of the lower canines, while fractures on the upper canines heal somewhat better. After transplantation of parathyroid bodies into the spleen or muscles of these parathyroidectomized rabbits the nervous manifestations disappear; the teeth resume their normal development, and only small calcium-poor zones remain as histological evidence of the former disturbance. But these dental regenerations cannot be produced by parathyroid feeding; neither has flooding the body of parathyroidectomized rats with calcium salts sufficed to cause retrogression of these symptoms. These facts prove that the parathyroids are indispensable for the assimilation of calcium. (Izumi, Farner and Klinger.)

What are the causes underlying these disturbances of calcium metabolism? We have already learned of the great disorders in protein metabolism which follow the removal of the parathyroid bodies. It has also repeatedly been shown that in these cases proteinogenous amins of most diverse sorts appear in the urine, and to the extent of giving it an alkaline reaction. Whether this greater formation of bases is to be regarded as a defense mechanism of the organism set up to neutralize the increased acid production, or whether the disordered desamidization of the amino acids constitutes the actual root of these disturbances is still a question to be solved. After the injection of beta-amidoazolethylamin (from histidin) symptoms similar to those occurring in tetany have been described, and many investigators consider this amin to

be identical with the hypothetical poison of tetany. From all the findings, the conclusion has been reached by more than one worker that the physiological function of the parathyroids consists in a detoxication of certain definite metabolic products of protein metabolism. According to one view guanidin constitutes the toxic cleavage product. The lethal symptoms which arise when serum from a parathyroidectomized animal is injected into a normal one have been held to support this view of the detoxicating function of the parathyroids. The well-known decrease which takes place in the irritability of parathyroidectomized animals upon subsequent removal of the thyroid may, in conformity with this hypothesis, be explained as a result of the lowered protein metabolism and the consequent decrease of toxic decomposition products brought about by absence of the thyroid.

Another explanation of parathyroid tetany is that after loss of the parathyroids an increased acid production leads to displacement of certain inorganic cations, especially calcium, from their inorganic compounds, and to their being flushed out of the body in the form of soluble salts of carbonic acid and phosphoric acid. But, all in all, these theories do not fautlessly explain all the known facts, and further investigations must determine whether the parathyroid function is one of detoxication or of true hormone action.

The thymus also plays an important part in calcium metabolism. Endeavors have been made to discover its physiological function through its removal. If thymec-

tomy is performed in young, sexually immature animals, there may be seen, after some four weeks, changes in the bones that greatly resemble those which occur in parathyroidectomized animals. The long bones of the extremities, in particular, become soft and pliable and show spherical swellings; the histological examination reveals an almost total absence of cartilage transformation into bone. Determinations of the calcium metabolism in such animals give a negative balance which is not altered by the administration of calcium salts, nor by the injection of juices expressed from the thymus; the total calcium content of the bones and tissues is also diminished.

Removal of the thymus after maturity entails no great disturbance, and even in youth the most conspicuous symptoms are the bony changes; no such manifestations of extreme irritability as follow parathyroid removal occur after loss of the thymus. All these findings indicate that the function of the thymus consists chiefly in promoting the assimilation of calcium salts by transforming them into substances which, like the colloid glycogen, will not readily diffuse out through the cell membrane. Whether these combinations of calcium are complex groups of carbonic and phosphoric acid compounds suited to bone building, or whether they are complex conjugated cell-colloid products remains for the present unknown.

The part which the germ glands play in calcium metabolism is, likewise, still unexplained; but that a connection exists between them and calcium assimilation may

be deduced from clinical observations pertaining to the ovary. Osteomalacia, a disease most frequent during pregnancy, is accompanied by an increased excretion of calcium and phosphorus in the urine and feces. This increase is considerably greater than the physiological increase always present in normal pregnancy. At the same time the quantity of these inorganic substances is also increased in the blood serum. From this the hypothesis has arisen that the increased internal secretion which presumably accompanies the visible multiplication of the specific interstitial cells is the factor underlying the greater calcium metabolism. This increased incretory activity was held to arise from an effort on the part of the organism to meet the increased calcium need created by the growth of the child. The cure of osteomalacia which quickly follows ovariectomy seems to support this theory of ovarian influence upon calcium metabolism. But it should be remembered that in pregnancy the secretions of the other endocrine glands are also altered; the hypertrophy of the thyroid has already been pointed out, and that loss of the thyroid secretion also upsets the circulation of calcium is shown by recent determinations of the composition of milk after thyroidectomy. Whereas in the normal goat's milk the ratio $CaO : P_2O_5$ is 100:100, after removal of the thyroid this ratio is changed to 100:160, with an increase in acidity from between 5 and 6 to 9. That the total calcium content of the milk is reduced after thyroidectomy and that there is also an absolute increase in its phosphorus is shown by the following figures:

TABLE IIIa.

Composition of Goat's Milk After Removal of the Thyroid (Grimmer).

	1 Liter Whole Milk			100 Grams of Ash		
	Ash	CaO %	P_2O_5 %	CaO g	P_2O_5 g	Ratio
Before operation	0.650	0.195	0.215	29.98	33.08	100:110.4
After operation	0.727	0.150	0.253	21.66	34.76	100:160.5

These results give additional support to the theory, that the regulation of calcium metabolism is not controlled directly by the ovaries, but that it takes place indirectly by way of the thyroid.

Here again let us call attention to the bearing of the ovaries upon the assimilation of iron. We have already seen that chlorosis, a disorder of puberty, is accompanied by an abnormally great excretion of iron, and that this may be compensated by the administration of inorganic iron salts; also that the synthesis of hemoglobin is not disturbed in this disease. Perhaps in this case the loss of iron takes place through another gland, the spleen, as there, according to Asher, a decomposition of red blood cells and a storage of the freed iron continually take place. The removal of the spleen in dogs is accompanied by an increase in the number of red corpuscles and of the hemoglobin content of the blood. Since, according to Asher's recent investigation, the thyroid is antagonistic to the spleen, the increased activity of the thyroid that occurs at puberty may be the cause of an increased iron elimination and of a diminished production of hemoglobin, resulting at times in chlorosis.

Iodine has a unique position among the inorganic constituents of the blood. It is found in traces in all the organs, but its greatest accumulation is in the thyroid; in 100 grams of the human thyroid an average of 10 milligrams of iodine were found, but the quantity varies with age and sex and is different in the inhabitants of different localities. The thyroid iodine of healthy cattle may vary between 0.023 to 0.468 percent; of pigs between 0.337 and 0.81 percent (Tatum). If one-half of the thyroid is removed the other half doubles its iodine store. The total quantity of iodine is also increased after feeding with inorganic iodine salts, and after such iodine feeding traces of iodine may be found for a long time circulating in the blood current. It has been determined, for instance, that the administration of sea salt to sheep increases the iodine content of the thyriod from amounts varying between 0.16 and 0.4 percent up to 0.71 percent.

Almost all the iodine in the thyroid is found to be incorporated within the protein molecule in an un-ionized form (Herzfeld and Klinger), and only very minute quantities, among which are traces of potassium iodide, are soluble in acetone. (Blum and Grützner.) If the thyroid is removed and transplanted to some other place in the body it does not thereby lose its capability of storing the circulating iodine, and it may still prevent all the symptoms generally produced by thyroid removal. The phenomena of iodine metabolism furnish another example of the efforts of the organism to prevent soluble substances that have been ingested in excess from becoming too concentrated in the blood and from being too

rapidly eliminated; this the thyroid accomplishes by transforming soluble substances into non-diffusible ones, thereby making it difficult for them to pass through the cell wall, and thus preventing their sudden inundation of the blood and their too rapid excretion. This evident part played by the thyroid gland in removing certain substances from active participation in metabolism appeared to sustain the older theories according to which the gland was regarded as performing only a detoxicating function. But the minute quantity of iodine circulating in the body makes it illogical to attribute to iodine poisoning the toxic symptoms which rapidly set in even in fasting animals from which the thyroid had been removed. The hormone nature of the thyroid secretion is to-day beyond discussion; the only question still left to be decided is whether the incretion is an iodine-containing combination (Baumann, Oswald, Kendall), or whether the iodine only stimulates the follicular cells of the thyroid to hormone production (Herzfeld and Klinger), the hormones themselves being only amins. (Abelin.) The latest investigations are not decisive as to the iodine content of the thyroid hormone; for many iodine-free preparations, as well as iodine-containing substances, are able to induce increased cell metabolism in thyroidless animals, and to hasten the metamorphosis of tadpoles. But, on the other hand, a direct participation of iodine in the composition of this internal secretion is indicated by the specific action of thyroxin, an iodine-containing compound isolated from the thyroid (Compare here chapter XI).

If we consider the metabolism of all the inorganic

substances from a common standpoint, we find that by the aid of hormones, the organism is making constant endeavors to de-ionize the inorganic salts and to transform them into colloidal combinations which become relatively inert through the great size of their molecules. For calcium metabolism it is the thymus and the parathyroids which are of the first importance; for iron, it is the spleen which influences the metabolism of this element, by way of the thyroid; for iodine regulation, it is the thyroid which evidently protects the organism from an excess of this element, and at the same time utilizes it in the manufacture of its own incretion.

4. *Water Control and Kidney Function*

Modern physiology considers the intake, the assimilation and the excretion of water primarily from the physiochemical standpoint and no longer regards purely physical laws as governing any part of the body's water metabolism. From investigations made by Van Bemmelen, M. H. Fischer, Hofmeister, Handovsky and myself, we know what complicated processes are connected with the fixation of water by the animal organism; that the water content of a tissue and its turgidity is dependent upon its content of inorganic salts, upon the hydrogen ion concentration of the surrounding media, and upon the relative proportions of the individual constituents composing its cell substances—proteins, fats, lipoids, etc. Hence it is self-evident that the great number of metabolic alterations produced by variations in incretory equilibrium also produce variations in the saturation of tissues,

so that the distribution of water in the organism becomes thereby an indirect function of the internal secretions.

The clinician is particularly familiar with the increased water saturation of the skin and subcutaneous tissue which occurs in persons with absence or under-functioning of the thyroid, as for example, in myxoedema. The scalp, the supraclavicular hollows, the nape of the neck and the dorsal surface of the hands and feet present tense, doughy swellings; pressure of the fingers in such places, produces impressions, different from those which are produced in genuine edema, where there is an accumulation of fluid in the interstices of the connective tissues. The older investigators believed that these skin manifestations in hypothyroidal states were due to the presence of "mucin." Even Falta thought it necessary to explain the negative results of many workers who had failed to find in the tissues evidence of a mucin-like material either by chemical or physical tests as having been due to fluctuations in this mucin-like substance during the course of the disease. But what was interpreted as a newly produced protein body, mucin, was due to an increased water absorption brought about by a change in the osmotic tension of the tissue, a change which causes the tissue to assume a gelatinous appearance resembling mucus. Whether this aqueous swelling is the result of the negative calcium balance commonly associated with thyroid deficiency, or whether the swelling is caused by an alteration in the composition of the blood plasma, brought about by the disordered protein and carbohydrate metabolism in this disease, we cannot

as yet fully decide. It is scarcely probable, however, that in the complex interplay of metabolic processes such a change in the absorption capacity of the tissue should be caused entirely by the lack of a single blood component, such as calcium. Positive proof that the thyroid actually

a b

FIG. 19. *a*. A 4½-year-old cretin with myxoedema. *b*. The same child at 5½ years, after having been treated with thyroid extract for 13 months (Honigmann).

initiates this disturbance of tissue water absorption is afforded by the treatment of myxoedema; for all these morbid manifestations in the skin and tissues disappear after the administration of thyroid preparations.

Of late years repeated attempts have been made to explain the secretion of urine as a pure, physio-chemical

process. It is possible to regard the excretion of water by the kidney as a purely physical phenomenon; the old Ludwig-Goll assumption that water is filtered under pressure through the constricted glomerular vessels, and that this filtration ceases when the blood pressure falls below 40 millimeters of mercury, is still a plausible explanation. We cannot, however, include all the other constituents of the urine as being subject, like water, to simple filtration. Evidence for the filtration hypothesis is seen in the influence of two incretory glands, the suprarenals and the hypophysis. It has been shown many times that adrenalin has a constrictor action on the smooth muscle fibres of the arteries of the kidney, whereas extracts of the middle and posterior lobe of the hypophysis diminish the arterial tonus. Adrenalin in quantities sufficient to raise blood pressure always increases the volume of urine; and the same thing occurs after extirpation or disease of the hypophysis, its inhibitory effect upon the suprarenals being then removed and the pressure in the kidney vessels correspondingly increased.

A hypophyseal disturbance well known to clinicians is the disease known as diabetes insipidus. In the publications of earlier writers we frequently find it stated that extracts of the hypophysis increase urinary excretion, a statement which seems contrary to our present knowledge. The investigations of recent years have shown, however, that the secretions of different parts of the hypophysis have different actions and give different results. Injections of extracts from the hinder part of the hypophysis, or preparations like hypophysin or pituitrin

diminish the quantity of urine and increase its concentration both in normal persons and in those with diabetes insipidus, the active portion of the gland, in this case, being really the pars intermedia (Leshke). Extracts of the anterior lobe have the opposite effect; they produce polyuria. Therefore, in functional deficiency of the middle and posterior lobe alone diabetes insipidus and polyuria results, but if the whole gland is diseased there may be no increase in the volume of urine excreted (Jacoby). Leschke found that five hours after injection with posterior lobe extracts the specific gravity of a normal urine had risen from 1.002 to 1.014, the sodium chloride from 0.078 percent to 0.426 percent and the urea from 0.125 to 0.525 percent.

Attempts have frequently been made to disprove that the internal secretion of the hypophysis is a causative factor of diabetes insipidus on the ground that it is possible, by isolated injuries affecting only the floor of the thalamus, and not the pituitary gland itself, to produce symptoms similar to those which occur in hypophyseal diseases (Bailey and Bremer). But these experiments still fail to prove that the symptoms produced by such means are not due to loss of pituitary function. For even if it were possible to carry out this operation without inflammatory conditions, the injured brain centers of the thalamus are not in a state to respond to stimulation by the secretions from the hypophysis and, for this reason, an injury to the thalamus or to the tuber cinereum becomes equivalent to extirpation of the gland itself. The positive fact that fresh hypophyseal extracts reduce

water excretion in pituitary disease is evidence of a more weighty character than operative findings interpreted to show that diabetes insipidus may be produced by injuries to parts of the brain lying near the hypophysis.

The tonus of the urinary bladder muscles is depressed by adrenalin, an effect similar to that produced by stimulation of the bladder's sympathetic nerve supply. On the other hand the contractions of the ureters are strengthened by adrenalin. These two different reactions to adrenalin constitute a purposive adaptation to the increased volume of urine excreted under the influence of adrenalin.

Numerous attempts have been made to prove that the kidneys are also glands of internal secretion. The favorable influence which injections of kidney extracts from healthy animals exert in uremia produced by kidney extirpation led to this supposition; the symptoms of uremia —unconsciousness, Cheyne-Stokes respiration, vomiting and distress—are said to be ameliorated and life is thought to be prolonged by such injections. Some authors have reported a rise in blood pressure of from 40 to 60 millimeters when kidney extracts were injected into healthy animals. Biedl described an increased lymph flow from the thoracic duct, reaching 8 to 22 times the usual outflow, after he had injected animals with an aqueous extract of kidney. But the reddish discoloration of this lymph and its admixture with erythrocytes pointed to another cause of the increased flow, that is, to injury of the capillary walls and a consequent increase

in permeability. On the other hand, increased blood pressure or increased lymph flow have never been observed after injections of venous blood from kidneys of healthy animals; the observations reported by Tigerstedt and Bergmann, who described a rise in blood pressure after injection of 2 cubic centimeters of the blood of nephrectomized animals, could not be substantiated by others (Lewandowsky). Moreover, union of the blood circulatory system of two rats did not prevent the appearance of uremia and oedema in one of them when both of its ureters were ligated. It is manifestly impossible to believe in the existence of such a kidney hormone, inasmuch as in this experiment the proof of an internal secretion of the kidney would lie precisely in the prevention of uremia in the one animal by hormones in the blood of the normal, uninjured animal. Against the supposition of an internal secretion of the kidney there is also the circumstance that the histological structure of this organ is neither of the type of the parathyroid, nor of the glious adrenal medulla, nor of the hypophyseal posterior lobe. Moreover, whereas disturbances arising from the extirpation of an endocrine gland may be prevented for a longer or shorter period by implantation of small portions of an identical gland, this has never been true of the kidney, as it has never been possible to amelilorate the symptoms of uremia by implanting kidney substance. On the other hand, it is a fact with which every clinician is familiar, that venesection and the use of diuretics may soon cause the symptoms of uremia to disappear. This fact furnishes conclusive proof, that

the morbid symptoms are not due to disturbance of an internal secretion of the kidney, but are the results of an accumulation in the blood and tissue cells of poisonous metabolic products which have not been excreted by the kidney.

5. *Activities of the Stomach and Intestines*

The intestinal movements which propel the contents of the bowel are of two sorts: a pendulous movement and a peristaltic movement. Both are brought about by contractions of smooth muscles of which there are two sets, one set running lengthwise of, the other about the circumference of the intestine. The movements are regulated by the central nervous system. Electrical or mechanical stimulation of the vagus nerve, below the branching off of the cardiac fibres, causes first a short inhibition, then a continually increasing acceleration of peristalsis; this experiment is certain to succeed only when the splanchnic nerves have been previously divided. We may therefore assume that the sympathetic nerve checks the contractions of the intestinal muscle cells, while the vagus accelerates them; in other words, the action of the sympathetic upon the muscles of the intestines is contrary to that which the nerve exerts upon the muscles of the abdominal arteries and upon the sphincters of the gastro-intestinal tract, the pyloric, the ileocecal and the anal sphincters. The action of the sympathetic may, as we have seen, be augmented by adrenalin; indeed, we know that after intravenous injection of this hormone, even in dilutions of 1:30 millions, a greatly diminished intes-

tinal peristalsis occurs, with paralysis of the circular fibres, strong contraction of the sphincters, and contraction of the intestinal blood vessels—a reciprocal action of different mechanisms extremely useful at certain periods of alimentary activity.

Here again, in the gastro-intestinal canal we may observe the same antagonism between the suprarenal glands and the hypophysis which we found to exist in their influence upon the kidney blood vessels; subcutaneous injection of pituitrin in dilutions of 1 part in 5,000 to 10,000 parts hastens intestinal peristalsis. Direct observations made through a celloidin window in the abdominal wall have confirmed these findings again and again.

Extirpation or hypofunction of the thyroid is always followed by constipation, and by feeding the gland or injecting its extracts this may not only be prevented, but it may even be replaced by diarrhea. The cause of constipation in this case is a diminished irritability of the vagus, and this irritability may be restored by thyroid preparations, a fact already mentioned in connection with iodothyreoglobulin.

Intestinal movements are not initiated by stimuli from the central nervous system, transmitted to the muscles along peripheral nerves, but the movements are only regulated by these stimuli; peristalsis goes on after section of the nerves, and even continues for a long time in isolated pieces of intestine preserved in a suitable manner. Even removal of Meissner's plexus does not interfere with the rhythmical contractions of the circu-

lar muscles, which cease to contract only after severance of the muscle connections with Auerbach's plexus; and longitudinal muscles still connected with their autonomic centers also continue rhythmical contractions.

These autonomic movements of the intestinal muscles may be influenced by hormones. Zuelzer, Dohr and Marxer and, later, Weiland, obtained from protein-free extracts of the intestinal mucosa a substance given the trade name *hormonal,* which, in injections of 10 to 20 cubic centimeters, greatly increases peristaltic contractions, and at the same time lowers blood pressure. The same increase in peristalsis is also obtained with splenic extracts—findings which led to the hypothesis that this incretion was manufactured in the gastric mucous membrane and stored in the spleen. Magnus and his fellow worker LeHeux have shown, among others, that the effective substance can be extracted from any part of the gastric or intestinal mucosa, and that the strength of the active principle may be increased 600 to 1,200 times by acetylization, or addition of the acetic acid radical; after injection of 2 milligrams of the isolated substance into a rabbit they obtained a fall in blood pressure to about 10 mm. of mercury, and the heart and respiration were affected as in vagus stimulation. The extract is inactive if applied to an isolated portion of the intestine from which Auerbach's plexus is removed, whereas pilocarpin, which directly affects the vagus ends and not the autonomic ganglia, does remain active.

The circle of proof that the hormone concerned in intestinal peristalsis is cholin was finally completed by

the isolation of this active principle and the preparation and identification of its double salts of mercury, platinum and gold. Its place of origin, however, is probably not the intestinal mucosa alone, for from the whole small intestine of a rabbit only 3 milligrams an hour could be obtained by dialysis; the suprarenal cortex and the spleen are especially rich in cholin and are probably the chief sources of this hormone, but it can be found in small amounts, also, in all the other organs.

Not only are the movements of the intestines affected by hormones, but the secretions of their mucous membranes are also under hormone influence. Adrenalin injections cause an increased flow from all the gastric and intestinal glands, analogous to the result obtained when the splanchnic nerve is stimulated. This increased flow occurs, even if the nerves supplying the alimentary tract are divided, so that here, also, the point of attack is the nerve endings, the myo-neural junction. In like manner the gastric secretion and the saliva are increased by adrenalin injections, and the bile also begins to flow from the hepatic ducts in greater quantity; this bile, however, does not enter the duodenum, but remains in the gall bladder whose muscles become paralyzed by adrenalin injections.

6. *Vitamines and the Endocrine Glands*

There is a group of substances most intimately associated with metabolism which are present in certain foodstuffs in extremely minute quantities. Although they neither provide protein material for the growth, repair

and replacement of living matter, nor furnish it energy like fats and carbohydrates, they are, nevertheless, indispensable to life, and in their absence certain definite disease conditions quickly result. These are the vitamines (Funk), nutramines (Abderhalden), or accessory food substances (Hofmeister). Some of the disturbances due to vitamine deficiency, such as pellagra, beriberi, scurvy and certain nutritional disorders of childhood, have long been known, but only recently have their causes been traced to the lack of definite vitamines in the food of sufferers from those diseases. The vitamines may be extracted from foodstuffs by water, alcohol, and other solvents; among their most aboundant sources are the husks, bran, and kernels of various grains. American investigators have given much attention to this field of research during the past few years and have divided the vitamines into three groups in accordance with their capacity to cure or prevent certain types of disorders. These are the antineuritic group, the antiscorbutic group and the antirachitic group. The corresponding disease states arise from feeding with vitamine-poor food which has been overheated or extracted, or from which vitamine-containing portions have been mechanically removed, as in the case of polished rice. The cure for such conditions consists either in administering normal foods or in supplemental feeding with substances containing the lacking vitamines.

Resemblance between the avitaminoses and various endocrine disturbances have recently received much attention. The fall in temperature in pigeons fed exclu-

sively on polished rice, the lowering of their blood pressure and their tetanic convulsions, phenomena pointing to a general disturbance of metabolic equilibrium, including a derangement of the internal secretions, were at first interpreted as consequences of a "polyneuritis," although it was not conceivable that an inflammation of the nerves could be healed within a few hours by injections of yeast or of bran extracts. When the discovery was made that these disturbances begin to abate almost immediately if rice polishings or equivalent portions of some other grain are added to the diet, the conception of beriberi as a disease due to some food deficiency was immediately confirmed. Pellagra, a disease of persons obtaining much of their protein from maize, of which the chief protein, zein, lacks the building stones tryptophan and lysin, greatly resembles Addison's disease. This resemblance led to the suspicion that the nervous symptoms in pellagra might be due to disturbances of the sympathetic system resulting from an insufficient production of adrenalin. This hypothesis seems to find support through pathological findings in the suprarenal gland of persons suffering from pellagra, for in this disease the average weight of the glands is less than normal (9.2 to 10.9 grams); the changes in the sympathetic system also resemble those found in Addison's disease, plasmolysis of the sympathetic ganglia, with atrophy of the non-medullated fibres produced by an hypertrophy of cortical tissue (Roaf). Also in the suprarenals of pigeons with an experimental avitaminosis produced by feeding them exclusively with polished rice similar

changes have been described by Kelleway and McCarrison; namely, an increase of the cortex at the expense of the medullary portion. Seaman has recently reported the cure of "polyneuritis" in pigeons through injections of acid alcohol extracts of thyroid; Funk and Douglas described degenerative changes of the endocrine glands, especially of the thymus, in beriberi. All these facts indicate a connection between the avitaminoses and the state of the endocrine glands.

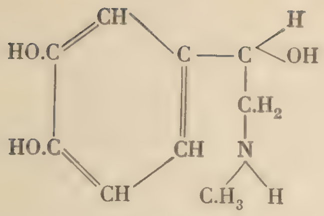
In explanation of these findings the suggestion has been made that perhaps the vitamines are precursors of certain incretions and that they derive their vital importance from this connection. Many foodstuffs contain amins with chemical structures that shows a close relationship to adrenalin. In Emmenthaler cheese, for instance, there is a large amount of tyramine, which, according to Abderhalden, may be regarded as the antecedent of adrenalin. The latter may be derived from tyramine by transposition of the side chain, as is shown in the following formula:

$$\underbrace{C_5H_4(OH) \geqslant C.CH_2.\underset{\displaystyle NH_2}{\underset{|}{C}}H.COOH}_{\text{Tyrosin}} - CO_2 \rightarrow \underbrace{\geqslant C.CH_2.CH_2.NH_2}_{\text{Tyramin}}$$

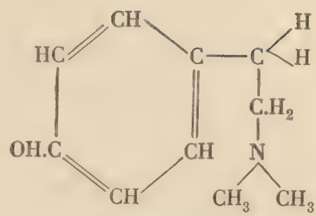
$$+ O \rightarrow \geqslant C.CH(OH).CH_2.NH_2 + CH_3OH \rightarrow H_2O - \underbrace{\geqslant C.CH(OH).CH_2.NH.CH_3}_{\text{Adrenalin side chain}}$$

5

In malt extracts, used very extensively by pediatricians as a vitamin source in milk diet disturbances of children, there is found a base hordenin, which is related to adrenalin even more closely than is tyramine. (Samelson.) This relationship is seen in the following formulas:



Adrenalin =
3, 4, Dioxyphenyl-methyl-aminoethanol



Hordenin =
4 Oxyphenyl-dimethyl-ethylamin.

But at present all these hypothesis have a very slender experimental support, and further investigations must be awaited before the relationship between the vitamines and the endocrine secretions can be explained.

7. *Metabolism and Muscular Activity*

Brown-Sequard laid the cornerstone of the science of endocrinology when in 1889 he injected himself with testicular extracts in order to put to the test the theory of internal secretions which he had propounded twenty years earlier. He described the changes produced by these injections as an increase in the general efficiency of his seventy-two-year-old body, with an improvement of appetite and of physical and mental vigor. His report regarding the specific effect of testicular extracts upon the functional capacity of the skeletal muscles met with great doubt and distrust. The increased muscular power was interpreted as the result of suggestive influences, and Forel even went so far as to describe Brown-Sequard's spermato-therapy as the product of a "senile-erotic imagination."

The basis of Brown-Sequard's announcement was fur-

nished by measurements made with the dynamometer. In 1860, then 43 years old, he was able to exert a pressure of 50 kilos; in 1863, a pressure of 46 kilos; in 1872, 37 kilos. The average of a great many trials made during the 10 days preceding his first injection of testicular extract, on May 15th, 1889, was 34½ kilos (32-37). Immediately after the first injection of a water extract made from guinea pig testicles, the dynamometer values rose to an average of 41, and reached a maximum of about 44 kilos, a value which still persisted when, three years later, a demonstration was made before the Paris Academy. Numerous experiments by other French and German physicians verified these findings. The following table gives a few of the early values obtained with the ergograph.

TABLE IV.

INFLUENCE OF INJECTION OF TESTICULAR EXTRACT ON MUSCULAR ENERGY.

Kilogrammeters	Subject	1st Period 6 days before injection	2nd Period During 10 days of injection	3rd Period 8 days after last injection
Minimum	I	8,036	8,525	9,857
	II	5,316	5,763	6,010
Maximum	I	9,525	9,823	10,821
	II	5,742	6,690	6,840
Mean	I	6,555	7,302	8,640
	II	4,497	4,866	5,550

Minima and maxima by Brown-Séquard; mean values by Copriati.

These figures made it obvious that the real increase in muscular capacity did not appear until 8 days after the injection. The objection was made that it was not at

all the effect of the testicular extracts which accounted for the increased muscular power, but that this was brought about by repeated exercises—a possibility which was known from many recent investigations in experimental psychology. Several years later Zoth and Pregl, working independently, repeated the experiments of Brown-Sequard with the ergograph, beginning their investigations under the influence of the same skeptical prejudice. They used subcutaneous injections of glycerine testicular extract which, after the addition of a 5 percent solution of common salt, was forced through a porcelain filter under a pressure of 50 atmospheres of carbon dioxide; 2 cubic centimeters of the extract were injected daily. They both found that the rise in the ergograph curve after the injections was by far higher than elevations obtained by long-repeated exercises. In one series of experiments on two students, A and B, who were not aware of the object of the experiments, one student, in order to test the possibility of suggestive influences, was given injections of pure glycerine only throughout an entire period.

When both these students were subsequently given testicular extract, Pregl obtained in student A, as a result of exercise, a 3.7 percent increase during the preliminary seven days of the test, and after the injection of testicular extract an increase of 23.3 percent. B first showed during a preliminary period of exercise an increase of 2.9 percent and a subsequent fall of 7 percent below the original value, but after the injection of testicular extract his muscular power increased to 9 percent above the orig-

inal value. These figures which have never been disproved fully verified Brown-Sequard's claims. Additional support of the truth of his theory was obtained through investigations which I made with Haupstein. Our experiments, conducted after long preliminary periods of exercise, when the increase in exercise efficiency had become constant, and interspersed with mock trials so as to exclude the influence of suggestion, showed an unmistakable increase in muscle strength on the day after the injection of fresh testicular extract.

TABLE V.

Influence of Testicular Extract on Muscular Work.—Dynamometer Readings.

	Right Hand Kilogrammeters	Left Hand Kilogrammeters	
Preliminary Period, 14 days	54.5–56 [1]	44.4–48.3	No injections
15th day	57.4 [1]	45.4	Injection of 1 ccm.
16th "	63.1	51.2	" " " "
18th "	54.8	47.0	No injections
21st "	55.5	44.3	Injection of 1 ccm.
23rd "	62.5	51.3	No injections
24th "	59.2	48.2	" "
25th "	56.8	48.3	" "
28th "	54.6	45.2	" "

[1] Average of 20 experiments.

I have dealt at length with the details of this work in order to show the close connection between these experiments and those recently published by Steinach respecting rejuvenation through an experimental revivification of the ageing puberty gland. He, too, found that after tying off the vasa deferentia, an operation which we will describe in detail later, there was—in addition to

the visible renewing of the fur and skin of the animals operated upon, and the reawakening of the sexual instinct—an increased capacity for muscular work. This increase was proved in rats subjected to the *strength test*. The rejuvenated males were able to jump down from a high beam or to climb up to a height in order to reach a morsel of bacon, while senile animals attempted to do so, but very soon sank back exhausted. Elderly men state that after the Steinach operation they are better able to endure long marches, stair climbing, and other tests demanding strength (Lichtenstern).

To what may be ascribed this increase in muscular capacity after injections of testicular extract or after the restoration of physiological function to the interstitial gland? According to Steinach rejuvenation is associated with a renewed acceleration of growth in all the organs, leading to restoration of their youthful elasticity; hence, the increased power of work might be due to the increase in muscle mass. There is, also, an increased sensitiveness of the entire nervous system, a fact which I was able to prove by injecting guinea pigs with testicular extracts. We may, on this evidence, consider the increased muscular power as analogous to those familiar exaltations of strength which take place when, through emotion, nervous excitation leads to extraordinary effort. Pregl demonstrated that after psychical excitement, such as was produced by an examination, the power to perform muscular work was increased.

The action of testicular secretions would, according to this conception, be similar to the effects of thyroid

preparations or of adrenalin which have more than once been spoken of; that is to say, in the results of testicular extracts we observe an action producing a lowered stimulus threshold for the same work production, or an increased work production brought about by the same stimulus. (Compare page 70.) Perhaps the effect of testicular extract may be produced only indirectly by way of the thyroid or suprarenals, the functional disturbances of which are known to lead to muscular dystrophy (Brock and Kay). The experiments of Grinker seem to speak in favor of this assumption. He observed a decrease in the exhaustion curve in isolated muscles after their inunction with extracts from either normal or Basedow thyroids. A similar energizing rôle is also ascribed to the synergist of the thyroid, the thymus, whose extracts likewise delay in frog muscles the exhaustion produced by rapidly succeeding stimuli. Del Campo believes that in this case the place upon which the incretion acts is the motor nerve endings.

CHAPTER VII

GROWTH AND BODILY FORM

1. *Growth of the Skeleton*

Characteristic of the living cell is: 1. Its tendency to grow, that is, to increase its mass by converting foodstuffs into its own substance, and: 2. Its ability to multiply by division. Even when separated from the organism of which they are a part cells may grow and reproduce. Carrel's experiments illustrate this fact exquisitely; he has succeeded in growing cells of many different tissues by keeping them in appropriate nutrient media, maintained at body temperature; according to the latest information, connective tissue has been kept growing in this manner over a period of seven years (Ebling).

Is this tendency of the cell to grow dependent upon some peculiar "growth energy," *i.e.*, upon a special life force, as the vitalists, Driesch and others, assume? Or do certain events, such as chemical, mechanical or other forces in the outer environment of the resting cell, so affect it as to cause changes in its osmotic pressure, which lead to an ingestion of food materials from its surroundings and to its consequent multiplication by division? Do all these events occur on the basis of physico-chemical laws only, as was maintained by Jacques Loeb? In this place we must content ourselves merely with pointing out

these qualities of cells, we must assume their capacity to grow as given, leaving the detailed discussion of the causes to books on general physiology. When cells are left to themselves, as happens when they are grown in the laboratory, we never obtain any organized living beings; for the creation of bodily form there is required, besides the coöperative action of different cell groups of various sorts, also the influence of certain definite factors, some of which are predetermined by inheritance, and others of which are produced by external circumstances. The study of the production of form and of the nature and significance of the individual factors which determine form, is the science of *developmental mechanics.* Its founder, W. Roux, differentiates three periods of form building: 1. The production of tissues and organs through inherited, form-determining factors already contained in the germ plasm and acting independently of the influence of function; also the development of a specific spatial arrangement produced in the embryo by segmentation and by the formation of the first organ anlages. 2. The coöperation of inherited, form-determining factors with stimuli that are produced by the functional activity of organs after the beginning of their histological differentiation. 3. Development of the final form of the organs and of the body through the influence of the various physiological functions. In this book we shall consider only the significance of the internal secretions as causative factors in form building; form-determining factors solely dependent upon inheritance will concern us only insofar as they may furnish proof of

how greatly the influence of endocrine gland functions upon the embryonic development in the second period is dependent upon primary inheritance factors contained in the egg.

The question of the real essence of form building will forever remain the deepest, most unfathomable problem of biology. Again and again investigators will seek to penetrate the marvel that from a little microscopic cell there may be produced a human being, built always upon the same plan, a plan which remains so constant through the ages that we find the same bones in the skeleton of a Neanderthal man as in a man of our own time; only the size of certain parts has altered in conformity with altered ways of living. How strong the growth impulse is, is shown by the fact that, to a certain degree, it is independent of nourishment; young dogs whose food is insufficient continue to grow in spite of it; they grow taller and longer, notwithstanding their increasing emaciation. The same thing may be seen among children of the poorer classes; during the four years of war, the average height of the German school children hardly diminished. Even the lack of particular foodstuffs does not prevent growth; young pigs fed upon calcium-poor food do not remain behind normally fed pigs in skeletal growth; their bones are merely softer and more pliable. How remarkably strong the growing impulse is may also be seen in the way that injured organs are perfectly repaired, or that totally amputated parts of lower animals are completely renewed in a short time. The chief internal factors which stimulate this cell growth and direct

it into definite paths are the glands of internal secretion. Added to these internal forces are many influences of an external nature, such as climate and food.

A short review of the development of the bony skeleton may enlighten us as to how the action of the incretions is manifested. The foundation of most of the bony skeleton is cartilaginous tissue which is formed from the embryonal gelatinous substances of the mesodermal layer by deposition between the proliferating cells of a hyaline cartilaginous gluelike material, chondrin. For certain definite bones, like the vault of the cranium, the parietals of the skull, the facial bones, connective tissue forms the foundation. In these two fundamental tissues, cartilage and connective tissue, bone develops by the deposition of calcium phosphate and calcium carbonate salts. In the long tubular bones the transformation of cartilaginous into bony tissue occurs simultaneously at two places; first, by a building of bony substance in the interior of the cartilage which is already arranged in a tubular form, *i.e.,* by endochondral ossification; and, second, by the formation of bone at the surface, or perichondral ossification. The latter process determines the thickness of the growing tubular bone, whereas its growth in length is dependent upon the multiplication of the cartilaginous cells lying in two definite zones situated between the shaft and the ends, namely, the epiphyseal junctions. The junction remains cartilagenous until the very end of the growing period, and in man ossification in the leg-bones, which determines the growth in height, is completed at about the twenty-fifth year. In the fingers and metacarpal bones,

it may be shown in the Roentgenogram, that the epiphyses disappear at the sixteenth or the seventeenth year, and in the other bones at about the twentieth year (Dieterle).

The connective tissue bones grow by the deposition of new osseous layers at their borders and on their surface and have no capacity to grow in length as have the tubular bones.

During the various stages of bone formation the glands of internal secretion have a decided influence upon the endochondral and periosteal ossifications, upon cell proliferation at epiphyseal junctions, and upon the final ossification of the junctions themselves.

Among the many abnormalities of thyroid origin, retardation of growth is the one best known to the clinician. If the thyroid is removed in a young dog or any other animal, a retardation in growth as compared with controls of the same age may be noticed within a few weeks after the operation. Not only is the development of the tubular bones retarded, but the skull also remains considerably smaller, more vaulted, rounder, with sharply sloping and vaulted frontal bones.

The same retardation of growth in height and of the skull occurs in human beings in whom the thyroids are absent from birth (congenital myxoedema). These conditions are also found when the function of the thyroid has been impaired by disease during early childhood (myxoedema; compare illustration 19). A table showing differences in height between healthy and myxoedematous children may illustrate these facts more clearly.

TABLE VI.

GROWTH OF HEIGHT IN CONGENITAL LACK OF THYROID (KASSOWITZ).

Age in Years	Height of Myxoedematous Subject cm	Height of Normal Subject cm	Difference cm	Underheight %
2½.........	72.	79.6	— 7.6	9.8
4¾.........	80.5	98.	—17.5	17.8
5¼.........	82.	101.	—19.	18.8
7½.........	83.	114.	—31.	27.2
10½.........	91.5	130.	—38.	29.6
12...........	95.	136.	—41.	30.1
20...........	116.	166.	—50.	30.1

In thyroidless herbivora and in subjects of infantile thyroid aplasia the bones are compact, broad and clumsy, while in the carnivorous dog deprived of the thyroid they are slender and narrow. In histological sections of such bones we always find as a typical sign the absence of ossification at the epiphyseal junctions, and in the Roentgen plate there is a lack of density of the bone shadows, particularly those of the wrist joints, giving evidence of retarded endochondral ossification.

Lack of the thyroid secretion is followed also by a failure of ossification in the cartilaginous sutures of the cranium, so that the cartilaginous synchondroses connecting the sphenoid and occipital bones may still persist in persons twenty years old. Manifestations of thyroid deficiency, therefore, are evinced not only in a defective endochondral ossification of tubular bones, but also in defective perichondral ossifications of flat bones. When we remember that in the absence of the thyroid

a *b*

FIG. 20. *a*. Radiograph of the hand of a 4-year-old child with congenital aplasia of the thyroid. *b*. Radiograph of the hand of a normal child of the same age. (Siegl.)

secretion the assimilation of calcium is also retarded, we have a partial explanation for the delayed ossification. The decrease in cell multiplication in the epiphyseal junctions, and the consequent dwarfing of the long bones may be accounted for by the diminished reactivity of these cells to nerve stimuli, a condition which, as we have seen, is also a consequence of thyroid deficiency.

The opposite conditions occur in cases of thyroid hyperfunctioning, as, for instance, in Basedow's disease, where the growth of bones in length and the closure of epiphyseal junctions by ossification is accelerated. Falta has described various cases of this disease with slender-skeletal-growth giantism, with swelling of the distal ends of the ribs, scapulæ and humeri, and a somewhat premature closure of the epiphyses. These changes are the result of increased nervous irritability which makes the cartilage cells, as all other cells, more sensitive to metabolic stimulation. The same phenomena of accelerated growth have also been described in experimental hyperthyroidism caused by feeding animals with thyroid substance.

The removal of the parathyroids is also accompanied by disturbances in growth, but these are attributed to diminished calcium deposition. The bones of such animals remind one of the bones of rachitic children, or the bones of adults suffering from osteomalacia. If the tibia in parathyroidless animals is broken in two halves a callus is formed by development of cartilaginous tissue at both fracture ends; but this union remains soft and spongy, and is never properly calcified and resorbed, as is the rule in healthy animals.

The thymus, the third of the endocrine organs having

a branchial origin, also influences calcium metabolism in the same way as do the thyroid and the parathyroids, and it has a similar effect upon growth in height. From this likeness of behavior one is inclined to assume that these three glands are related functionally as well as embryologically. The influence of the thymus continues until puberty when it is checked by the ripening germ glands (compare illustration 24). An indication of the changing rate at which the thymus participates in growth is seen in the variations in weight which its parenchyma undergoes throughout life. Its weight, according to Hammar, is 12.33 grams in the new-born, 25.18 grams at the fifteenth year, when a rapid falling off occurs until, by the end of the twentieth year, its weight is only 12.71 grams; at the forty-fifth year it is but 2.89 grams, and at seventy-five years the parenchyma is found to be completely atrophied.

Removal of the thymus in adult animals is, accordingly, without influence upon growth in height. Klose and Vogt found that after the twentieth day the thymus could be removed from dogs without producing changes of any kind, but its extirpation in dogs ten days old was followed by retardation in growth of the long tubular bones. These showed rachitic-like bowing, were easily breakable and, when broken, exhibited poor and retarded callus formation at their fracture lines, changes similar to those known to occur after parathyroidectomy. Certain observations of a character contrary to these findings remain, up to the present, still unexplained; Coutiere, for instance, found that young thymusless chicks showed rapid increase in weight and size.

The changes in bone following thymus removal are to be attributed to lack of calcium deposition; even the vertebræ of such animals are so soft that they can easily be cut. Transplantation of the thymus from another animal, or regeneration of the gland from small post-operative rests is followed by the disappearance of the morbid symptoms, an indication that their appearance was due to lack of the thymus incretion.

An antagonism also exists between the germ glands and the hypophysis, as there does between the germ glands and the thymus. After removal of the hypophysis, the testicles of young cocks increase in weight more rapidly than do the testicles of controls. According to Foa the averages were 8 and 5.3 grams respectively; he found a corresponding increase in the size of the seminiferous tubules. Loss of the testicles produces a corresponding acceleration in growth of the hypophysis; the hypophysis of capons weighed 0.25 grams, six months after castration, those of normal cocks 0.13 grams (Massaglia). In rats, also, development of the testicles is accelerated by removal of the hypophysis; within a month the testicles become heavier by about 50 percent than those of normal rats, but later they begin to lag behind normal testicles in growth, so that after 48 days the difference is again equalized. Hyperpituitarism, as should be expected, retards sexual development. Goetsch found this to be so by feeding young rats with the anterior lobe of the pituitary. Growth of young dogs in height is retarded by removal of the hypophysis; they remain strikingly behind their brothers and sisters in growth; the bones of their extremities become clumsy

and crooked, and histological examination shows nonclosure of the epiphyseal junctions; the small skull has the same rounded infantile form as that of the thyroidless dog. All these occurrences may be retarded for some weeks by transplantation of an hypophysis into the abdominal wall or into the bone marrow, another proof of the internal secretory function of this gland.

Fig. 21. Left, skeleton of a dog killed at 12 months of age from which the hypophysis had been removed when 2 months old. Right, skeleton of control of the same age. Their weights at the time of operation were 4 and 3.4 kilos, respectively. A year later the weights were 4.3 and 16.3 kilos. (Aschner.)

The morbid condition known as acromegaly, which is often associated with tumors of the pituitary, is supposed to be due to hyperfunctioning of the hypophysis. This supposition is in harmony with the synchronous increase in the number of acidophile cells seen in its anterior lobe, and also with the acceleration of growth that takes place in rats fed on the anterior lobe of the hypophysis. The posterior lobe, however, is said to retard growth in rats

(Goetsch), an observation which von Uhlenhuth verified on salamanders. According to other investigators implantation of or feeding with pituitary gland produces results the opposite of those just described (Wulzen), and some workers have obtained no results whatever (Klinger). For the present, therefore, we have no well-defined understanding of the action of the hypophyseal secretion upon growth.

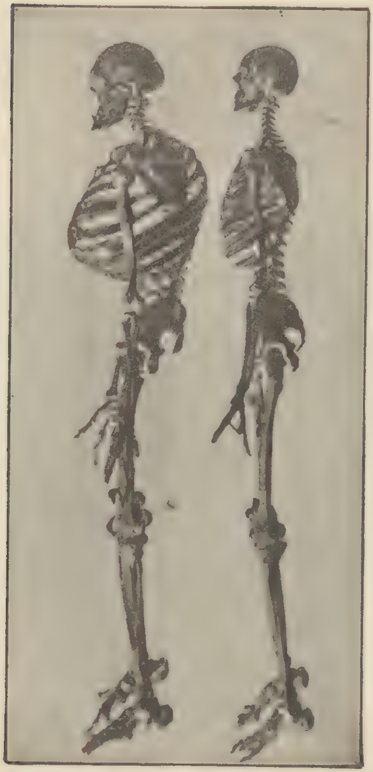


FIG. 22. Normal and acromegalic skeletons. The latter shows deformity of skull, protrusion of the chin and of the parietal emithe limbs and especially of the nences. Deformity of the thorax and spinal column; elongation of hands. (Leri.)

There is occasionally, without overfeeding, a sudden increase of bony growth in children, that is considerably in excess of what is typical for the family and race to which they belong. This gigantic growth is observed most frequently in boys at the period of puberty; their lower extremities begin to grow more rapidly than their arms, which retain a normal relation to the trunk. Such giants may reach a height of two meters by their twentieth year and they may continue to grow through another period even beyond the twenty-

fifth year, because their epiphyseal junctions remain open. However, the second period of growth differs from the first one in that this second growth is limited mostly to the ends of the extremities; hands and feet become clumsy in appearance; the disproportion between the large head and other parts of the body becomes conspicuous even to the layman; acromegaly has developed after gigantism.

Such abnormal growth of the extremities may also occur after the height attained is only normal and it is then always connected with some change in the hypophysis: enlargement produced by hypertrophy of its specific glandular cells. Removal of the hypertrophied portion leads to the disappearance of these symptoms, so that here again there is evidence of a connection between the incretion of the hypophysis and the growth of bones.

The antagonism of the germ glands to the hypophysis is shown in the accelerated growth in height which occurs after castration, an acceleration achieved by a more rapid cell proliferation and a retarded calcification in the epiphyseal junctions. Men castrated before puberty differ from men of their locality by their enormous height. Tandler and Grosz described various members of the Russian sect, Skoptzy, who, for religious reasons, perform castrations on very young boys. In these children the puberty period passes without any specific evidences whatever; the ordinary normal changes in voice, growth of hair, sexual desire, etc., do not take place, and the thymus also fails to regress as it does in normal children. The following table of normal body measurements gives material for comparison with abnormal conditions.

TABLE VII (VIERORDT).

	Man	Woman	Newborn Boy	Newborn Girl
Standing Height	167.8 cm	156.5 cm	55. cm	50. cm
Sitting Height	98.5 "	93.7 "	34. "	31.5 "
Leg Length	103. "	98.4 "	.. "	.. "
Shoulder Girth	39.1 "	35.2 "	12.76 "	12.43 "
Hip Girth	30.5 "	31.4 "	10.62 "	10.3 "
Weight	65. K	55. K	3.33 K	3.20 K

In eunuchs we find standing heights of 180 to 200 centimeters, but only in those who were castrated before the cessation of growth; castrations made after the twenty-fifth year are without influence upon body length. In cases of arrested development of the male sexual glands, such as occurs in eunuchoids, an abnormal body length is also attained in most of the subjects in whom the atrophy was prenatal. (Compare illustration 16.) The same phenomena are found in the female sex; standing heights of 179 centimeters, and more, are reached in cases of inhibited ovarian development.

In all these subjects longitudinal sections and X-Ray plates of the bones show a characteristic persistence of the epiphyseal junctions, and a lack of ossification in these zones, presenting a contrast to the pictures of too early closure produced by sexual precocity. It was found, for instance, that in a precocious girl, who at 13½ years possessed all the sexual characteristics of a mature woman, there was complete closure of the various epiphyseal junctions, and the X-Ray plates showed all the bone shadows complete. In a nine-year-old boy with

hypertrophy of one testicle there was a development of all the male sexual characteristics and a height of 143 centimeters; in the girl the height had become stationary at 131 centimeters (Krabbe). Besides such cases where growth and height is associated with injury to or absence of the germ glands, there are recorded many cases of male gigantism with absolutely no anomalies of the male sexual characteristics. The older authors endeavored to explain these cases as instances of a peculiar growth energy acquired through inheritance. Re-examination of these records, and the more searching investigations of recent years, have shown that in these cases of gigantism there must also have been a period of arrested germ gland development, with a retardation of puberty until the eighteenth year, so that up to that time the thymus and the hypophysis were not restrained by the germ gland incretions from exercising their accelerating influence on the growth in height. On the other hand, many cases of dwarfish growth show unfailing evidences of developmental disturbances of the thyroid and hypophysis. From all these facts we are, in the light of our present knowledge, justified in concluding that physiological growth in height is regulated by the internal secretions.

There remains now to be considered the bearing of the suprarenals upon growth and development. The embryological relationship of the suprarenals to the gonads explains certain parallelisms in the functions of these two glands; why, for instance, in connection with the cyclical changes occurring in the ovary and uterus during menstruation and gravidity there are also simul-

taneous periodic changes in the cellular structures of the suprarenals (Kohn). In precocious puberty, with an accelerated and quickly completed growth in height, the suprarenal cortex as well as the gonads hypertrophy. In this regard, however, there seems to be some difference between the two sexes, as this acceleration of puberty is more common in girls than in boys, the ratio being 14: 3. Some sex-linked differences in functioning seem already indicated during the developmental period of the suprarenals; in the male guinea pig the histological structure of the gland shows little change after its embryonal period, whereas the female suprarenal undergoes the cyclical modifications already mentioned as occurring in menstruation and pregnancy.

The relations of the various endocrine glands to growth in height is shown in a schematic way in Figure 23, on the following page.

2. *Rapidity of Growth*

The preceding examples have already shown us that growth is not influenced by the different endocrine glands acting independently of one another, but that, on the contrary, they must coöperate in their activities in order that the human body may be harmoniously formed. Such coöperation is exemplified most clearly in the antagonism that exists between the thymus and the germ glands in their influence upon growth. The thymus is the gland of growth in childhood; according to Dehmel, an over-supply of thymus tissue produced by transplantation of this

gland into three-weeks-old rats leads to an acceleration in growth of length, recognizable in the broad epiphyseal junctions. With the beginning of puberty the thymus gradually diminishes both in its absolute weight and in the mass of its secretory parenchyma, its growth becom-

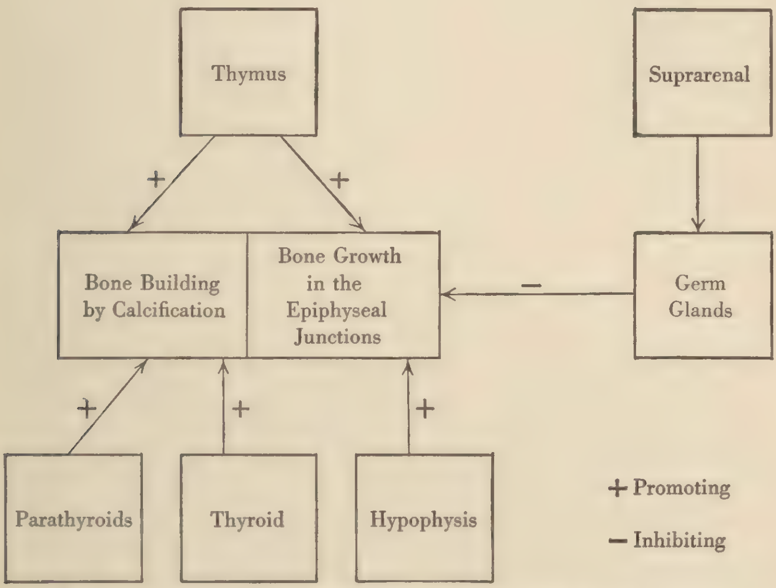


FIG. 23. Schematic Representation of the Action of the Internal Secretions on Growth in Height.

ing minimal at the period of the maximal development of the germ glands. With these events, as we have already seen, the proliferation of cells in the epiphyseal junctions ceases and ossification is hastened. This relationship between body growth, thymus, and germ glands is illustrated in the following curve:

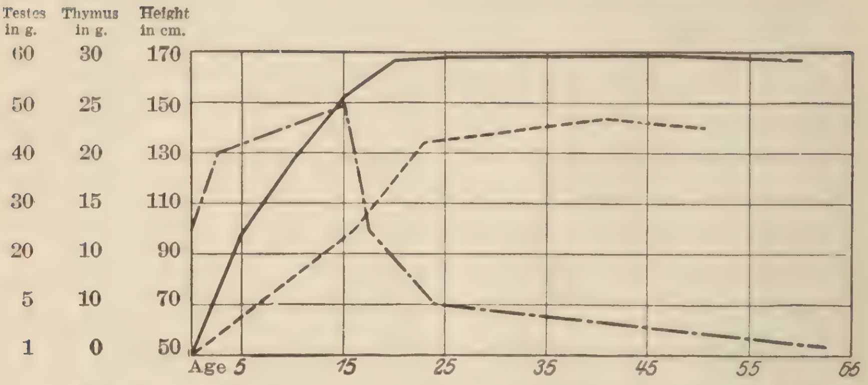


FIG. 24. Age in years, represented on the abscissa; body height, on the ordinates. Weight of testes and thymus expressed in grams. Continuous curve (—) = body length; (------ curve) = testes weight; (—-—-—-— curve) = thymus weight.

Rapidity of growth is also dependent on external causes of the most varied character. Among these may be mentioned influences of a social nature, differences in nourishment, climate, racial peculiarities, and other conditions. Nourishment as a factor of growth received special attention during and after the war. During this time, observations showed that ossification occurred earlier in city than in country children; evidence of this was seen in an increased calcification disclosed by the X-Ray. Coincident with this accelerated ossification there was also a more rapid growth in height.

"Environmental influences" are, according to Stettner, the results of climatic stimuli. Children of the well-to-do classes in the large cities are, as a rule, anxiously sheltered against every change of weather. They grow up like hothouse plants in a constant temperature, whereas

children of the poor and country children are exposed to frequent changes from hot to cold; greater demands are thus made upon their vaso-motor system, resulting in a better adaptation of these children to external surroundings. That such climatic influences affect growth not only through action on the central nervous system but also by way of the endocrine glands is shown by C. Adler's investigations upon the origin of metamorphosis in amphibia. Retardation and acceleration of metamorphosis in the amphibia have been explained by two opposed theories. According to one theory, "exogenous" factors, such as climate, amount of water, character of the land, food, etc., were considered the ruling forces; by the other theory "endogenous" causes, comprising innate tendencies, particularly those of hereditary origin, were assumed to be paramount; and after the discoveries of Gudernatsch the internal secretions came to be thought of as the sole cause of the amphibian metamorphosis. Both hypotheses were supported by numerous facts, and it was, consequently, necessary to discover the connection between the exogenous and the endogenous factors. It was known from older experiments that raising the temperature from 10° to 16° C. hastened the exit of larvæ from the egg membrane and the subsequent metamorphosis. It was observed by O. Hertwig that Rana temporaria grew twice as fast at 25° as at 16° C. If frogs and larvæ are bred at higher temperatures than the optimum of 25° C., then their growth and metamorphosis is slowed back toward the normal rate; at the same time, in young animals, a retardation of the growth of the thyroid also

occurs, while in mature frogs changes in its colloid material and atrophy of its follicles take place. If the experimental animals are kept at a temperature of 8° to 10° C., permitting the thyroid to develop normally until the larvæ have reached a length of 22 millimeters, and the embryos be then exposed to a temperature of 31.5° to 30.5° their metamorphosis becomes accelerated, but their development remains stationary at a stage which corresponds to the degree of atrophy of the thyroid. In a third series of experiments the animals were first bred at the injurious temperature of 31.5°, and after their metamorphosis was thus hastened it was completed at an environment of 10°, at which temperature the thyroid was able to recuperate and to develop normally, as was seen by the structure it had attained at the completion of the experiments—increase in the size of the gland, enlarged epithelial cells, enlarged follicular spaces, etc. (Fig. 15 a-c.)

The accelerating action of the thyroid on the entire metabolism, as we have already come to know it, furnishes an explanation of the connection between the optimum temperature, the increase in the size of the gland and the acceleration of metamorphosis. Through the energizing action of the thyroid hormone the larval organs are dissolved and serve as building material and sources of nourishment of the other body cells, thus meeting the increased needs of these during this period of heightened activity in the life of the animal. A support of this explanation is seen in the retardation of metamorphosis brought about by feeding the tadpoles

abundantly on a diet rich in proteins. In these circumstances, increase in size becomes possible without a simultaneous scarcity of protein material that would lead to digestion of superfluous larval organs.

Artificial thyroid hyperfunctioning was first induced in frog larvæ by Gudernatsch, who fed them on fresh mammalian thyroid gland. He found, as have a number of later observers (Romeis, Abderhalden and Schiffmann, Jarisch), that metamorphosis was thereby greatly accelerated, but that growth was retarded; the larvæ developed into frogs earlier, but were smaller than their controls. After 30 days of thyroid feeding the tadpoles measured 131 to 265 millimeters, the controls 228 to 283 millimeters (measurements of 29 animals, Abderhalden). Along with this inhibition of growth a modification of form takes place; the hinder part decreases in circumference and at times a constriction develops between thorax and abdomen, giving the larva a fiddle-like appearance. Along with the accelerated transmutation of the omnivorous larva into a carnivorous frog there is a precocious absorption of the horny teeth and of the lip papillæ, and the growth of the under jaw is hastened; the intestine also participates by the development of a stronger musculature, and the liver by changes in its histological structure. A characteristic feature is the early appearance of the fore limbs, the left appears first as usual and before the loss of the tail (Cotronei). The tail muscles disappear through phagocytosis, carried on by the greatly increased number of leucocytes which show numerous mitoses, while erythrocytes show by their

numerous irregular nuclei that rapid division is also taking place in the bone marrow (Lim).

Instead of thyroid substance, thyroxin has been given and found to accelerate metamorphosis in thyroidless axolotls—a proof that this substance is, as Kendall as-

FIG. 25. Influence of the thyroid and thymus on metamorphosis. Frog larvæ 4 weeks old. *a*, normal tadpole; *b*, animal fed 14 days with thymus; *c* and *d*, fed 21 and 14 days, respectively, with thyroid gland. (Abderhalden and Schiffmann.)

sumes, the specific incretion of the thyroid gland (C. O. Jensen).

Thymus feeding has the opposite effect; it retards metamorphosis and hastens the growth in length. After twenty days of feeding with fresh thymus the length of

the animals thus fed was 275 to 389 millimeters, while controls measured 212 to 292 millimetres (Abderhalden, 30 experiments, Fig. 25). A nucleo-protein prepared from the thymus gland by Romeis greatly diminished the number of defective larvæ which ordinarily develops from each spawn, and deformed larvæ, fed on it for twelve days, surpassed normal controls in length by 2 to 6.6 millimeters.

Greatly increased growth but without essential acceleration of metamorphosis has also been observed after feeding with hypophysis and testes. Feeding with testes produces striking slenderness of the trunk and great delicacy of the extremities (Stettner). Feeding with the anterior lobe of the pituitary hastened growth in length of axolotls, after metamarphosis but not before (Amblystoma opacum); lengths of 138 millimeters were reached by axolotls fed on anterior pituitary tissue, whereas the average length is 115 millimeters (Uhlenhuth).

We have gone so extensively into these experiments concerning the metamorphosis of the frog for the purpose of showing that when the environment retards or accelerates body growth the functions of the endocrine glands are first altered, and that changes in these glands and their functions are in themselves adequate to bring about the transformations that were previously attributed to endogenous influences arising in the body cells. When we regard the influence of nourishment upon the development of the human body from this standpoint we may, perhaps, conclude that certain "constitutional anomalies," "diatheses," and "nutritional disturb-

ances'' are also to be explained as products of altered internal secretions, and that they need not be attributed to an exceptional reactivity of the protoplasm, predetermined by an inherited disposition. In the example of milk-feeding disorders, and their cure by means of malt extract, it has already been indicated how the relation between growth and nutrition may be mediated through the internal secretions.

3. *Shoulder and Pelvis Breadth*

Measurements of the breadth of the human body are made mostly on the basis of the circumference of shoulders and pelvis, and the development of these parts are dependent on the male and female germ glands. In this connection the figures in Table VIII are instructive:

TABLE VIII.

Pelvic Measurements Made by Vierordt and Tandler and Grosz

	Man	Woman	Eunuchoid 28 years old and 181 cm high
Distance, in centimeters, between the sup. ant. iliac spines	24.4	26.	22.
Transverse diameter	12.8	13.5	12.
Conjugata vera	10.8	11.6	10.7
Oblique diameter	12.2	12.6	r 12.5 l 12.2
Distance between the ischiad spines	8.1	9.9	9.3

We see from the figures that the female pelvis is especially adapted to its physiological function as a birth canal; whereas in man it narrows from above downward, in woman it remains almost the same breadth throughout its length. In man the canal, seen from above, is elongated and compressed laterally; in woman it is more nearly circular, approaching a transverse oval. The angle formed by the two rami pubes is, in the woman, very nearly a right angle; in man, the angle is more acute. The promontorium extends sharply forward in man; in woman it is flattened down so as to form no obstruction to the passage of the child. In the female pelvis the bones are delicate and smooth; in the male they are heavy and rough. These differences in human pelves also exist more or less distinctly in other mammals. The female form of the pelvis becomes more accentuated by gestations, for during this period the parts adapt themselves to fit their physiological functions. In children these differences between male and female pelves are not yet developed; the child's pelvis, seen from above, is rounded; its form is between that of the adult male and female; the bones are soft, the epiphyseal junctions still open.

That the changes in the pelvis at the onset of puberty are actually induced by the internal secretions of the germ glands, and not by hereditary dispositions of the germ plasm, is shown by castration experiments of many different kinds; by substitution of absent gonad secretions through implantation of glands from other animals; by

Fig. 26. *a*, male; *b*, female pelvis. (Rauber-Kopsch.)

injections of extracts of these glands. The drawings on this page showing pelves of normal and of castrated sheep illustrate some of these points. They represent

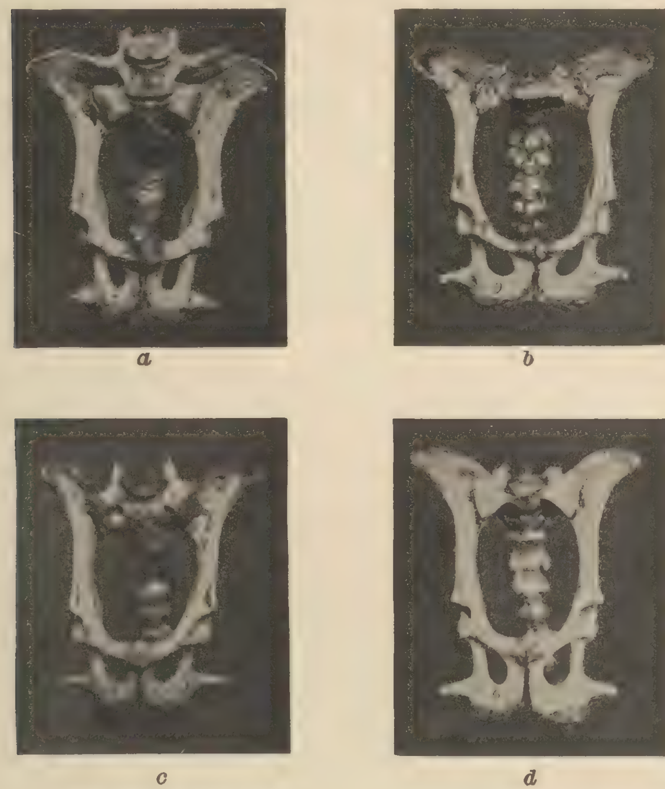


FIG. 27. *a*, Pelvis of a two-year-old male sheep; *b*, pelvis of a female sheep of the same age; *c*, pelvis of a two-year-old male sheep, castrated at one month; *d*, pelvis of a female sheep of the same age, castrated at the same time. (Franz.)

pelves of two-year-old lambs (*d* and *c*) which had been castrated at the age of one month, and pelves of two noncastrated lambs (*a* and *b*) of the same age. The

pelves of the castrated sheep are nearly alike both in weight and form; the diameter of the male pelvis is less than normal, but the size of the outlet is above normal; the female pelvis, on the other hand, has a narrower outlet and a smaller diameter than the normal female pelvis. Both pelves of the castrated sheep have forms which lie between that of the normal male and female forms; they have remained at an infantile stage, representing asexual immature forms. Similar retardation occurs in castrated individuals of other domesticated species; the skeletons of castrated cows approximate those of oxen; the pelvis of castrated horses of both sexes retains an infantile rounded form, and in the male the anterior projection of the pelvic junction, characteristic of the stallion's pelvis, is lacking. In castrated human beings similar changes are produced; the pelvis is small and rounded with an obtuse pubic angle.

The same pelvis form is developed in eunuchoids in whom hypofunction of the germ glands is congenital. (Compare Fig. 28.) The shape which the pelvis assumes in castrated human females has not yet been accurately described, but it is known indirectly through observations of pelves in subjects of female infantilism. Hyperfunction of the ovaries, as we have already seen, may produce in the adolescent girl a pelvis form characteristic of a completely mature woman, and in some cases ossification of the epiphyseal junctions takes place at 11 to 13 years of age. Steinach's transplantation experiments on guinea pigs and rats have furnished additional proof that the

sexual differentiation in the form of the skeleton is brought about by the internal secretions of the germ glands. The normal adult guinea pig is in all respects larger and heavier than the female of the same age; early castration removes the restraining influence upon growth exerted by the ovaries at the time of puberty and permits the castrated female to grow larger than her sisters. (Compare Fig. 36.) If glands from the opposite sex are transplanted into young castrated animals, the female with a well-ingrafted testis in her body develops like a male; and the male containing an ingrafted ovary in its abdomen remains retarded in growth and acquires a feminine form.

Further proof of the dependence of pelvic development upon the internal secretions of the germ glands is shown by the acceleration of pelvic evolution produced by injections of ovarian extracts into young animals. Plant succeeded in producing precocious changes in the rabbit by means of lipoid-free extracts of cows' ovaries; after nine injections the narrow pelvis of a rabbit twelve weeks old had developed into a rounded form and the angle between the pubic processes in the symphysis had become broader.

Sex differences of the same sort occur in the formation of the thorax, which ordinarily is broader and more strongly built in the male than in the female. The relative breadth of shoulders and pelvis in normal and eunuchoid human adults is shown in the following table:

TABLE IX.

RELATION OF SHOULDER, PELVIS AND HIP MEASUREMENTS.

	Shoulder Breadth cm.	Pelvis Breadth cm.	Hip Breadth cm.	Ratio of Pelvis to Shoulder	Ratio of Hip to Shoulder
Man	39.3	29.	31.8	100:135	100:123
Woman	35.	30.	34.	100:116	100:103
Male eunuchoid...	36.8	27.	31.5	100:137	100:117
Female eunuchoid.	37.	26.5	34.	100:140	100:109

(Pelvic breadth is the diameter between the outer borders of the iliac crests; hip breadth is the distance between the two trochanters of the femurs.)

Subnormal development of the male germ glands leads to arrested development of the thorax, and the proportions of the eunuchoid trunk approximate those of the female. The relatively greater circumference of the eunuchoid female pelvis is caused by the more exaggerated deposits of fat at the hips. In domestic animals, also, we may observe the greater development of the male thorax, which on account of the more strongly developed muscles of the male appears even relatively larger than it actually is as compared with the female thorax. The chest measurements in immature males lie between those of the adult male and female, and castrated forms approximate the infantile asexual type.

4. *The Architectural Plan of the Entire Body*

Anatomists and artists have always endeavored to condense into a single formula the relations between its various proportions which give harmony to the body, and to show that definite laws governed the relative dimensions

of the parts of the human form. Vitruvius, the Roman architect, discovered that the length of the entire body was eight times the length of the head and sixteen times the length of the foot. Zeising, a German investigator of the first half of the nineteenth century, maintained that all the body measurements, both the long and the cross-sections of its parts, have to one another ratios which correspond to the law of the mean proportional. Schmidt and Liharzek arranged a "key to bodily proportions," based upon the distance between the points of rotation of the separate joints. And many artists, Michael Angelo, Leonardo da Vinci, Dürer and others expressed more or less fanciful notions concerning the harmony of the human form, though without being able to find an exact mathematical formula which would include all cases.

Nevertheless, what we designate as a well-proportioned body must have certain definite ratios between the measurements of its separate parts. These ratios vary, it is true, with race, climate and other conditions, but for man and woman there are constant, narrowly limited differences characteristic for each sex. These differences are manifested most clearly in the relative lengths of the upper and lower parts of the body and in the proportions between the lengths of the limbs and the total height.

In the following table in which the body proportions between man, woman and eunuchoid are compared, the standing height represents in centimeters the distance between the vertex of the skull and the surface upon which the subject stands in the erect posture; the sitting height is distance from vertex to tip of coccyx in sitting posture.

TABLE X.

BODY PROPORTIONS OF MALE, FEMALE AND EUNUCHOID.

	Man[1]	Woman[1]	Male[2] Eunuchoid	Female[2] Eunuchoid
Standing Height	164.9	153.6	190.	175.
Sitting Height	86.6	82.4	88.	79.
Arm Length	74.4	67.6	82.	85.
Leg Length	85.9	78.7	102.	96.
Ratio of Standing to Sitting Height	100:52	100:54	100:46	100:45
Ratio of Standing Height to Arm Length......	100:45	100:44	100:43	100:48

[1] Weissenberg.
[2] Author's measurements.

The results of removing the germ glands have, indeed, shown that these definite, sexually-determined proportions are intimately associated with the internal secretions. The ratios of standing height to arm length are strikingly constant for normal men and women, as they also are for eunuchoids of both sexes. But in the latter, the absence at the time of puberty of the growth-inhibiting action of the germ glands, and the persistance of open epiphyseal junctions beyond the twentieth year, leads to the excessive growth in leg length which is a typical characteristic of hypofunction of the germ glands and of early castration. The figures for male and female eunuchoids in the preceding table show a striking correspondence in the lengths of the upper and lower body

a *b*

Fig. 28. *a*, Skeleton of a normal man; *b*, skeleton of a male eunuchoid. Eunuchoid from Tandler and Grosz.

parts (100:116; and 100:122), and the same approximate equality is shown in the values recorded in other literature (Tandler and Grosz give for male eunuchoidism and female infantilism the ratios of 100:126 and 100:127). We find, therefore, fairly constant ratios which express relative proportions typical of the asexual body form, just as there are constant ratios typical of normal male and female body measurements. In the lower animals the same change in the ratio of upper to lower body lengths is produced by castration; it is manifest in the tall ox and the long-legged gelding, both of which closely resemble castrated females of the same species.

We saw in a former chapter that the more rapid growth in length of castrated animals can be traced to an accelerated cell multiplication at the epiphyseal junctions, brought about by increased stimulation coming from the hypophysis after the germ glands with their growth-inhibiting function had been removed. This assumption of greater hypophyseal activity is supported by the histological evidence of increased cell proliferation seen in the enlarged hypophysis of castrated animals. The other glands of internal secretion are more or less indirectly implicated in the sexual differentiation of the body form, but the leading rôle is always played by the germ glands. Consequently in their absence there results an infantile type which is the expression of a completely altered and disordered coöperation of the remaining endocrine glands.

5. *Secondary Sex Differences*

In conformity with the old belief in a nervous regulation of life processes, earlier investigators sought to explain the differentiation of sex by assuming differences in the brain development of the two sexes. Gall maintained that in the newborn the cerebellum was but slightly developed, bearing to the entire brain a proportion of one part to between nine and twenty parts; that after puberty this ratio became one to from five to seven, and that the ratio of cerebellum to whole brain became smaller in man than in woman; he also maintained that in persons castrated young the cerebellum remained in its infantile stage of development; that the distance between the two mastoid processes furnished a measure for determining the development of the cerebellum; and that the greater the sexual differentiation the greater became the distance between the mastoid processes. These teachings, after their publication in 1810-1819, fell into obscurity, and remained so until their revival by Möbius and Bunge some twenty years ago. But at present there is grave doubt concerning the validity of Gall's theories; further evidence is needed to prove the existence of such a relationship between the size of the skull, the relative weight of brain parts, and the dependence of these upon the presence and sex of the germ glands. Some old determinations of brain weights of the horse made in Gall's time will serve to illustrate his theories.

TABLE XI.

FIGURES ILLUSTRATING GALL'S THEORY OF RELATIONS BETWEEN BRAIN WEIGHTS, SEX AND CASTRATION.

(LEURET, MARCHANT AND LASSAIGNE; BUNGE'S PHYSIOLOGY).

	Entire Brain gm.	Cerebrum gm.	Cerebellum gm.	Medulla gm.	Ratio of Cerebrum to Cerebellum
Stallion	534	433	61	40	7.07
Mare	498	402	61	35	6.59
Gelding	520	419	70	31	5.97

In the bull also, the powerful development of the back head with its broad muscular neck is very conspicuous as compared with the same structure in the ox and the cow. However, even there the figures fail to supply unimpeachable support of Gall's theories.

In the foregoing text examples were shown which prove without question that the differentiation in the skeleton of the two sexes is dependent on the germ glands. The loss of these glands gives a preponderant power to the other endocrine secretions, with the result that a skeletal structure is formed which has neither a masculine nor a feminine form, but an asexual one. This skeleton is characterized above all by relatively equal lengths of the upper and lower body parts. Yet in spite of their likenesses male and female eunuchoids show essential and characteristic differences. Their germ glands, though atrophied, have still the recognizable morphologic structure of ovary and testicle; the penis, prostate and seminal vesicles, and the uterus, vagina and pubis are developed

to a certain degree. The question therefore arises, are these sex characteristics independent of the germ gland incretions, or does the meagerly developed interstitial tissue suffice to produce the different sexes from an asexual embryonic form? Before this question can be answered we must consider the problem of the determination of sex in general. The question whether sex is determined during, before, or after the fertilization of the egg has been answered in many ways. One view is that the fertilized egg is already sexually differentiated, and that the spermatozoon can exercise no influence upon sex determination (Lenhossék). Opposed to this view is the belief that there are two kinds of spermatozoa, one kind containing an even number of identical chromosomes, the other kind containing an equal number of chromosomes, one of which is anomalous in size and shape, and that union of the ovum with one of these kinds of spermatozoa results in female offspring, while union with the other variety of spermatozoon produces male offspring (Guyer, Wilson). The unmistakable phenomena of two kinds of spermatozoa has lately been observed in many animal species, and has made the view that sex is determined at the time of fertilization almost unconditionally accepted. If that be the case, the question then arises whether the whole body form is determined at the time of fertilization, or whether the differentiation concerns the germ glands only, while the somatic cells are given their specific imprint by the functioning of the germ glands at a later period? In answer to this it may be stated that we know from embryological studies that the first

organ anlages differentiated from the primary germ layers show no discernible sex differences, and that in both sexes the development of the uro-genital apparatus begins with the formation of the primitive excretory organs, the pronephros and the mesonephros and the efferent Wolffian duct from which the duct of Müller is later split off to end in the uro-genital sinus; whether or not the anterior end of the Müllerian duct arises partly from the mesonephros also is not definitely known. During the splitting off of the duct of Müller, when the human embryo is about 22 millimeters long, the germinal epithelium of the body cavity, which up to that time has remained undifferentiated as to sex, begins, along the median border of the pronephros, to form the specific germ glands; before that time it is impossible to say whether an ovary or a testicle will be formed (O. Hertwig).

If we adopt Roux's three periods in the development of form (see page 142), this stage in the differentiation of the germinal epithelium will coincide with the opening of the second period, during which the congenital determinants begin to coöperate with stimuli produced by the beginning functional activity of the differentiating organs. The gradual transformation of the ducts of Wolff and Müller into efferent ducts of the germs glands takes place as follows: In the future male the duct of Müller atrophies, and from the Wolffian duct the seminal vesicles with the vasa deferentia and paradidymis develop. In the female, the duct of Müller becomes the oviduct; the Wolffian duct disappears with the exception

of a part which becomes the epoophoron. Of these structures the germ glands are primary, the ducts secondary sex characters. So long as the relationship between the genitals and the internal secretions was not known, the external as well as the internal genitals were classed among the primary sexual characters, and only the other sexual characters were regarded as secondary; development of these secondary characters was thought to be controlled by the germ glands, whereas the development of the genitals was believed to be predetermined in the egg. (Hunter, Darwin.) Poll endeavored to make a causal classification of the different sex characters by distinguishing some characters as "essential" and others as "accidental." The former, the essential characteristics (germinal), were the germ glands; the latter, the accidental characteristics, he divided again into *auxiliary-genital* and *extra-genital,* each of these consisting of *inner* and *outer* factors. The inner factors of the auxiliary-genital class were the germ gland ducts (oviduct, vas deferens), the uterus and the accessory genital glands; the outer factors were the penis and vagina. The inner factors of the extra-genital constituent were the psyche and the voice, the outer factors, the hair, horns, etc.

In our own future treatment of this subject we shall make use of the conception of Tandler and Grosz, which, in addition to other proofs, has received great support through Steinach's investigations. According to this view, except the germ glands all characters that differentiate the two sexes are secondary; originally, all

these were somatic characters, owing their evolution and structure to the harmonious coöperation of the glands of internal secretion; the soma cells were, therefore, an originally asexual embryo which took on its sexual stamp only under the influence of the internal secretions (Lipschütz).

We shall now undertake to follow, in both sexes, the various sexual differentiations of the separate organs, as these differentiations are influenced by the action of the internal secretions. Some of the transformations from the asexual type into the male and female form we have already considered in the discussion concerning the development of the skeleton, and the change from the boy's to the man's voice. Other sex variations are the different male and female blood pictures, the peculiarities of their body temperature, and other distinguishing phenomena among which one, very striking in our longitude, is the difference in the growth of hair. In man, the pubic hair is very marked; it extends upward to the navel in a concave or triangular form; breast and face are also hairy. In woman, the pubic hair forms a triangle with the base above, either slightly concave or straight; the body hair is generally scant, the face hairless.

The direct dependence of hair growth upon the internal secretions of the germ glands can be shown by the removal of the ovaries and testes. Male eunuchs have smooth, hairless bodies; their pubic hair is poorly developed and resembles the pubic hair growth in women; the axillary hair is also scanty, and on the face hair is

absent or nearly so. In female eunuchs the pubic hair is lacking; on the chin there are a few hairs, such as develop in old women and male eunuchs.

FIG. 29. Member of Russian sect, Skoptzy, castrated in childhood; 24 years of age. (Tandler and Grosz.)

The loss of hair following thallium administration is an indirect proof of the relationship between the internal secretions of the testes and the suprarenals; for in addition to the loss of hair, thallium also causes atrophy of the testes with loss of the sexual impulse, and a decrease in the adrenalin content of the suprarenal glands. (Buschke and Peiser.) That the secretions of the testicles furnish the initial stimulus to hair growth is shown by the excessive development of hair characteristic of male sexual precocity. In a nine-year-old boy with a tumor of the left testicle, the hair and beard resembled that of an adult; after removal of the left testicle the beard fell out; the body hair diminished; only the pubic hair

remained (Falta). In cases of late castration, the body hair and beard fall out; implantation of a normal testicle is followed by a return of hair growth. The stimulus which arouses the hair cells to increased activity does not seem to reach them from the internal secretion of the testes direct, but appears to come indirectly by way of the suprarenals. Evidence of this is furnished by the peculiar hair growth in diseases of the suprarenal cortex. In young girls of 7 to 19 years, and occasionally in old women, tumors of the suprarenal cortex lead to a marked development of beard, and sometimes to a growth of hair over the whole body (hypertrichosis, hirsutism). Simultaneously with the hypertrichosis there occurs an atrophy of the ovaries and the internal genitals, with arrest of menstruation. Whether this atrophy of the ovaries is a consequence of the altered function of the suprarenals, or whether the loss of the germ glands removes an inhibiting influence on hair growth, presumably exerted by the suprarenals, it is difficult to decide; for such hirsutism is said to occur in abnormalities and neoplasms of the ovaries. The increase in abdominal hair during pregnancy which is associated with an increase in the size of the suprarenal cortex is also an example of the incretory relationship between the suprarenals and the germ glands. These organs, we have already seen, are embryologically related; they arise from adjacent regions of the celome and show a histological resemblance, especially between the cells of the suprarenal cortex and the cells of the interstitial germ gland tissue; in community of origin and similarity of

structure there is, consequently, a natural basis for a functional relationship between the ovaries and the suprarenal glands. In this connection an observation of Friedenthal may be of interest; in the "melanodermatous (dark) races," the woman closely approximates the man in regard to hair growth, and in this feature she bridges the gulf between the two sexes. This becomes of special interest when we take into consideration the rôle played by adrenalin in the production of melanin, if we suppose that increased outside temperature is associated with a change in the function of the suprarenals. There may be in this respect a relationship between climate and suprarenal gland function similar to that which Adler's work has shown to exist for the thyroid. In his more recent work, making use of the older investigations of Hertwig, Adler has shown the influence of the internal secretions upon the determination of sex. He believes that an actively functioning thyroid is a factor for maleness, inasmuch as males predominated in a race of frogs from the Ursprungstal, which at the age of half a year had large, Basedow-like thyroids. In experiments with frogs' eggs that had remained for different lengths of time in the female body he found that eggs fertilized when over-ripe gave a preponderance of males, and these males developed hypertrophied thyroids which showed an overgrowth of the follicular epithelium and liquefaction of the colloid.

The internal secretions regulate not only the hair growth of human beings, but also the feathers and hair coverings of other vertebrates. The castrated capon is

differently feathered from the cock. He is, however, more and not less abundantly feathered, thus reversing the condition shown in the hair growth of human castrates. There is in the capon a more exuberant growth of the neck and tail feathers and a more brilliant coloring of the rest of the plumage (Poll, Sellheim). Inasmuch as a cock-like growth of feathers occurs in old hens, we may assume that in this species the ovary inhibits the growth of feathers. In the capon, the comb and wattles which are characteristic of the cock shrink, but the great spurs are not affected. Ovariotomy causes the spurs to enlarge and become like those of the cock, thus showing that the intact female germ gland inhibits the growth of the spurs. Morgan made very interesting experiments on a hen-feathered strain of campine cocks. After castration these cocks grew feathers with typical cock-feathered markings. It was found that the interstitial tissues of the testes in this hen-feathered strain contained large cells heavily loaded with fat, such as are normally present in the luteal cells of the female ovary. On the other hand, implantation of a testicle into a caponized domestic fowl causes a growth of the comb which exceeds the growth of combs in normal cocks. From a breadth of about 60 millimeters in castrated males the comb became 80 to 145 millimeters broad after the implantation, whereas it was only 80 to 110 millimeters broad in the normal cock (Pezard). This result could be achieved with even half a gram of implanted testicle tissue. Lipschütz was actually able to prevent the formation of the castrated type by leaving within the body of the animal operated

upon the one-one-hundred and fortieth part of the original testicular substance. From these findings Pezard concludes, that the morphogenetic effect of the testicular incretion is not a quantitative reaction, but that it follows the law of all-or-none.

The rough coat of the male guinea pig is markedly different from the fine, smooth fur of the female and serves to distinguish the one from the other; but the fur of a castrated male resembles the female covering. It is, therefore, apparent that in the male guinea pig, as in man, the genital glands produce a stimulating effect of the hair cells. An analogous fact has been observed in the cervidæ in which the growth and shape of antlers is dependent upon the testes. Experiments of Tandler and Grosz have shown that the antler changes are dependent upon the time of castration; if the animals are operated upon at a time when the newly formed horns are still covered with velvet the results are different from those obtained if the testes are removed after the velvet has been torn and stripped off by brushes and brambles. In the first case the horn forms by hypertrophy a wig-like antler resembling a tumorous mass; in the second case the horn is first shed and afterward a deformed one is grown. In the female deer astration has no influence on antler formation, which indicates that only the testicular and not the ovarian incretions have power to further this function.

In the human race there also exists between the two sexes a difference in the degree of horny growth; the

nails in man are generally coarser and thicker than in woman. Esbach gives the average thickness in the male sex as 0.384 and in the female 0.346 millimeters; but occupation naturally plays a great rôle in determining nail thickness.

The sexual characteristic hitherto considered are, making use of Poll's classification, of the extragenital order or type. In regard to the dependence of these on the germ glands, the recent accumulation and analysis of experimental material has left scarcely any differences of opinion. There is, on the contrary, no such unanimity in regard to the development of the accessory structures. In the case of the efferent ducts of the germ glands we have already discussed the probability of their having been formed by an incretory action exerted by the recently differentiated germinal epithelium upon the asexual anlages of the Müllerian and Wolffian ducts. The penis and the clitoris are derived from identical anlages, the former by rapid, the latter by slow growth. Their development begins in human embryos of 11 to 13 millimeters length, when there is formed at the anterior end of the still closed cloaca a thickening produced by hypertrophy of primitive connective tissue; this, the genital eminence, begins to show a differentiation at the fourth month after impregnation. In the female embryo the anterior end of the eminence slowly thickens to form the clitoris; in the male embryo a rapid growth in length of the genital eminence produces the penis. On its lower surface the genital eminence is divided by a cleft which is bounded by two folds of skin. In the female these two parts of

the genital cleft, the phallic folds, form the labia minora; in the male they constitute the two lips which fuse to form the corpus cavernosum urethræ. From the folds of the skin which surround the genital eminence there develops the labia majora of the female and the scrotum of the male.

The embryological development of the copulatory organs has been dealt with thus extensively because the knowledge will be very useful in helping us, later, to understand hermaphroditism. The table on page 188 by Hertwig shows the sex differentiation of the common asexual anlages.

When castration takes place before puberty further development of the penis is inhibited; hence, in adult eunuchs and eunuchoids this organ may be scarcely two centimeters in length. Its erectile tissue, compared with that of the normal corpus cavernosum urethræ, remains undeveloped, and the carvenous spaces are encroached upon by an ingrowth of new connective tissue. Lipschütz regards the production of this new tissue as evidence that these conditions in the penis result from disuse atrophy due to lack of sexual activity, and not to a direct action of the germ glands. In cases of congenital atrophy of the ovaries the external genitalia remain likewise undeveloped (Fig. 41).

A similar picture is seen in rats from which the testes are removed at six to four weeks; the penis remains at an infantile stage and lacks the glans. Castrated guinea pigs and rabbits show the same lack of development; the penis, prostate and seminal vesicles are dwarfed to one-

TABLE XII.

Showing the Structures Developed from the Primitive Asexual Anlage (Hertwig).

Male Sexual Parts	The Common Form From Which Both Arise	Female Sexual Parts
Seminal ampullæ and seminal tubules	Germinal epithelium	Ovarian follicle, Graafian follicle
	Primitive Kidney	
(*a*) Epididymis with rete testis and tubuli recti	(*a*) Anterior part with the sexual cords (sexual part)	(*a*) Epoophoron with medullary cords of the ovary.
(*b*) Paradidymis	(*b*) Posterior part (the real mesonephric part)	(*b*) Paroophoron
Vas deferens with seminal vesicles	Mesonephric duct	Gartner's canal, in some mammals
Kidney and ureter	Kidney and ureter	Kidney and ureter
Hydatid of epididymis. Sinus prostaticus (Uterus masculinus)	Müllerian duct	Oviduct and fimbriæ Uterus and vagina
Gubernaculum Hunteri	Inguinal ligament of primitive kidney	Round ligament and ligamentum ovarii.
Male urethra pars prostatica and membranacea)	Sinus urogenitalis	Vestibulum vaginæ
Penis	Genital eminence	Clitoris
Pars cavernosa urethræ, Scrotum	" folds	Labia minora
	" ridges	Labia majora

tenth the size attained by the normal animal. In rabbits in which unilateral castration has been performed the growth of the penis is proportional to the amount of interstitial tissue in the conserved testicle, and it is independent of spermatogenesis (Fig. 30-34). In human be-

Fig. 30. Testis of a 6½ months rabbit, castrated on one side 5 months previously. The normal penis of post pubertal form is represented in Fig. 34. Fully developed spermatogenesis is seen in the canaliculi; the seminal vesicles contain spermatozoa; the interstitial cells have large, spherical nuclei and abundant cytoplasm. (Fixed by Helly's, and stained by Heidenhains method.)

ings, on the contrary, infantile genitals have been found associated with well-developed Leydig cells (Berblinger). The question whether "the incretion arises from the spermatogenic or from the interstitial cell portion of the testicle," has, therefore, not yet been definitely answered.

The effects of the germinal incretions on the growth of genital structures were shown by the transplantations of testes into castrated animals which were carried out by Steinach on rats and guinea pigs, and by Voronoff and Lespinasse on men. These effects were also shown by

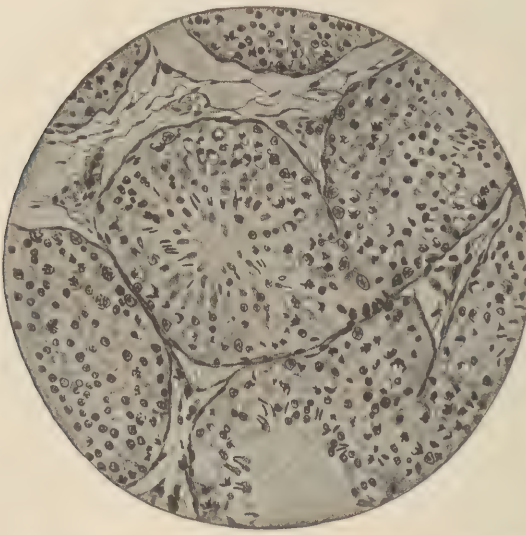


FIG. 31. Testis of a 6½ months rabbit castrated 5 months previously, from the same litter as in Fig. 30. Fully developed spermatogenesis in canaliculi; spermatozoa in seminal canals; interstitial cells poor in cytoplasm; small nuclei; cells with elongated nuclei predominate.

Ancel and Bouin with subcutaneous injections of glycerine extracts of cryptorchoid testes into castrated guinea pigs; after nine months the penis of these castrates had attained almost the length of a normal organ (3.2 centimeters in castrates, 3.7 centimeters in normal guinea

pigs), whereas in the non-injected castrates the organ had shrunk to 2 centimeters in length. But the seminal

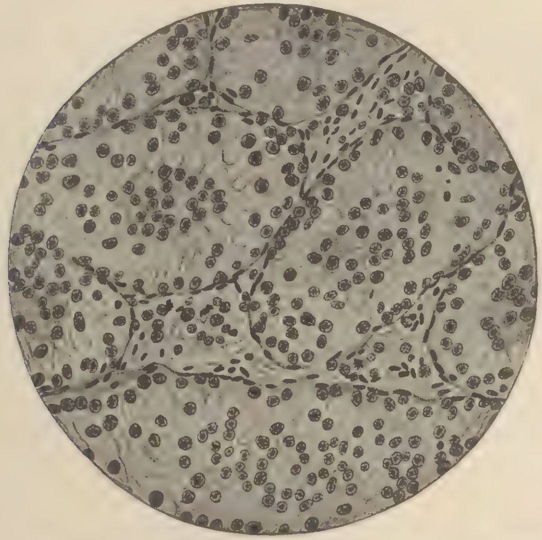


FIG. 32. Testis of a 7½ month rabbit in which at the age of 2 months a horizontal section was made through the testicle without injuring the ductus epididymus. The penis, which was normal at 4 months, began at the beginning of the 7th month to undergo pubertal changes at a rate greater than normal. The development of the canaliculi has continued, but without normal spermatogenesis. The canaliculi contain numerous cells that may be Sertoli cells; cells that may be spermatogonia but not spermatocytes. Widespread desquamation; interstitial cells with very abundant cytoplasm and large spherical nuclei; mitoses in interstitial cells. (Fixed according to Bouin; stained with hæmotoxylin-eosin.)

vesicles in the injected animals did not recover their normal size, the respective lengths being: normal 5.8 centimeters; injected, 3.6 centimeters, and castrated, 1.3

centimeters. Nature performs the same experiment on precocious children. For example, in a boy of ten months,

Fig. 33. Section of testis remnant from an 8-months rabbit from which, at 4 weeks of age, one entire testis and half of the remaining one had been removed; penis infantile; diameter of canaliculi double their size in a rabbit of two months; many cells that may be Sertoli cells; numerous spermatogonia. Desquamation in many tubules; absence of normal spermatogenesis. Interstitial tissue of a pubertal character; cells very poor in cytoplasm; nuclei small; connective tissue cells predominate. Figs. 30-33 are preparations and drawings by Wagner, from the work of Lipschütz, Wagner and Borman. (Fixed according to Helly; stained by Heidenhains method.)

with testes as large as hazel nuts, the penis was already 5 centimeters long, though the body weight was only 7.9 kilos and the height 72 centimeters.

6. *Transformation of Sex*

The hypothesis that the germ glands govern the formation of the sex characters has received its convincing proof from the experimental sex mutations which Steinach, Athias and Sands have made on rats and guinea pigs, that Brandes has made on deer, and Goodales and Pezard

a *b* *c*

FIG. 34. Penis (*b*) of rabbit, the testicle of which is represented in Fig. 31, compared with the penis (*a*) of a castrated rabbit and with the penis (*c*) of a normal rabbit. *a*, penis of a 7½ month rabbit, completely castrated 5½ months previously. (*c*) of a normal rabbit.

a. Penis of a 7½ month rabbit, completely castrated 5½ months previously.

b. Penis of a rabbit with testis (Fig. 31) in full spermatogenesis with interstitial cells poor in cytoplasm and having small nuclei. Cells with elongated nuclei predominate. The penis shows an infantile form; the glans (outgrowth of the corpora cavernosa) is lacking.

c. Penis of a normal rabbit from the same litter as *a* and *b*, life-size, drawn from living animal; *b*, drawn from preserved preparation, consequently somewhat shrunken. (Lipschütz, Wagner and Bormann.)

on the domestic fowl. The germ gland transplantation experiments of W. Schultz, Bucura and others had furnished the preliminary groundwork for these investigations. In a preceding chapter evidence was shown that the generative portion of the female germ gland, the

ovum, is not the only portion of the ovary which takes part in the development of the ultimate body form, but that the corpus luteum also produces a secretion concerned with this function, Steinach and Holzknecht gave additional proof of this by excluding the influences of the generative tissue of the ovary by means of the selective action of X-rays. Female guinea pigs of from two to four weeks received a dorsal radiation of 11 to 12 Holzknecht current units, in dosages of 7 to 8 Bauer unit penetration with hard unfiltered rays. Three or four weeks later a slight loss of hair was apparent, and in eight weeks a marked exaggeration of certain female characters had taken place. In 40 percent of these guinea pigs the nipples of the young virgins had grown to a size normal for pregnant females, and for a period of three or four weeks their breasts secreted milk of normal color and fat content. Histological examination of the ovaries showed a complete atrophy of all the follicles, and the "ovarian stroma throughout almost its whole mass had been penetrated and filled in by an enormous overgrowth of the female puberty gland cells," which in their size and lipoid content corresponded to the lutein cells of a corpus luteum. In older virgin animals that were given the same X-ray treatment the results were not so conspicuous; in some of them the ovaries showed connective tissue degeneration, making evident the fact that to produce the same effect in younger and older animals different dosages of X-rays are required; the consequences in the older guinea pigs were similar to the effects produced by castration, that is, dehydration with

reduction in the size of the nipples, and complete atrophy of the mammary gland tissue.

Of late, Roentgen radiation has been much used for the control of ovarian bleeding. In many of these cases,

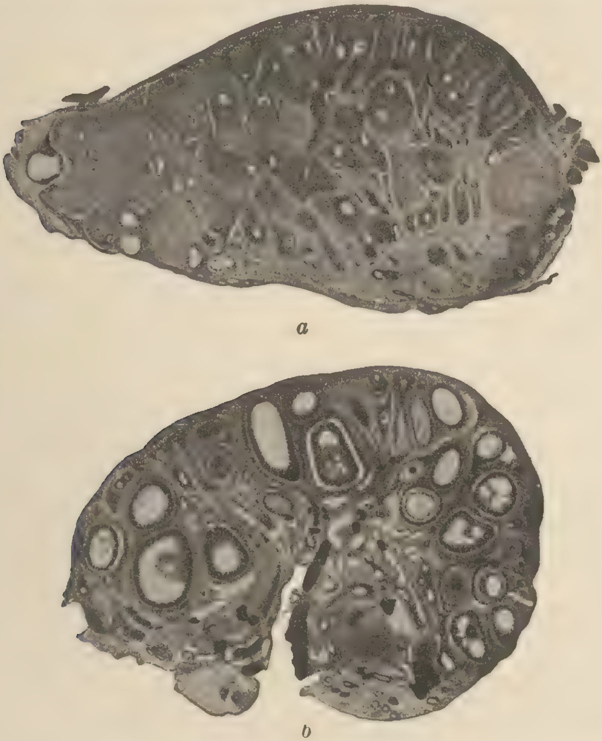


FIG. 35. *a*, Section through the ovary of a 4½ month guinea pig treated with Roentgen rays at the age of 3 weeks. *b*, Ovary of a normal sister from the same litter. (Steinach.)

also, tension of the breasts and secretion of colostrum has been observed; and it may be predicted that in the future when autopsy records of such cases have accumulated they will describe the same histological changes

that occur in Roentgenized guinea pig organs. Injury to the reproductive part of the testicle has been reported in men whose calling has exposed them much to the X-rays. Inasmuch as these reports relate only to adults in whom all the sex characters are already fully developed, they have not yet yielded much information concerning changes in sex characters produced by X-ray injury of the male generative cells.

Hypertrophy of interstitial tissue, with complete conservation of spermatogenesis, has been observed in guinea pigs that showed recognizable signs of precocious sexual maturity, such as has often been described in children of both sexes. In children, however, the coincident changes in the germ glands have not been so thoroughly investigated. It would be of the greatest interest to determine whether in these cases, too, precocious maturity goes parallel with over-development of the interstitial cells. Such precocious male guinea pigs are distinguished by an earlier growth of hair, a more rapid increase in weight and length, particularly of the head, and an earlier, more complete development of the corpora cavernosa of the penis and of the accessory genital glands than occurs in their brothers of the same age. These animals also show a premature awakening of sexual desire; they are more aggressive, and attempt coitus even with females in heat; the histological picture of their testicles shows the sperm canals to be well developed and spermatogenesis to be normal, while the cells of Leydig are increased in number and form greatly thickened nests and clusters.

Steinach's work received its actual impetus from his experiments on transplantation of germ glands into castrated animals. He found that after healing took place, the generative portions of the transplanted ovary and testis always degenerated, whereas the interstitial cells rapidly multiplied and usurped the place of the atrophied sperm canals and follicles; the renewal of lost male or female characteristics by the implantation of a germ gland could thus be logically attributed to the increased incretory activity produced by the multiplication of interstitial cells. Steinach did not stop at homologous grafting, but undertook by means of heterologous grafts to completely change the sexual characteristics of animals of one sex into those of the opposite sex. The results which he obtained are illustrated in Fig. 36.

The upper row shows a guinea pig family of one brother and three sisters. Two of the three sisters were castrated and into one of them the testes of an adult male guinea pig were engrafted beneath the skin of the belly. This *masculinized* female began two weeks later to develop the same shape, the same coarse fur and the same psychical sex characters as her brother from the same litter, and in the course of her further development she surpassed him in all masculine attributes. *Hypermasculinization* had occurred, and through the histological findings it could be traced to hypertrophy of the interstitial cells.

In the second row, the third picture shows a male castrate into which ovaries were engrafted. The inhibitory influence of the female germ gland upon the growth of

(*a*) Masculinization

Masculinized Sister | Castrated Sister | Normal Sister | Normal Brother

(*b*) Feminization

Castrated Brother | Normal Virgin Sister | Feminized Brother | Normal Brother

Fig. 36. Upper row: 1, masculinized sister; 2, castrated sister; 3, normal sister; 4, normal brother. Lower row: 1, castrated brother; 2, normal virgin sister; 3, feminized brother; 4, normal brother.

the skeleton and its determination of the external body form is here plainly manifest. Analogous to the preceding case, a *hyper-feminization* had been produced; development of the nipples and hypertrophy of the milk glands, more rapid than in the virgin sister of the same age, was so great that the teats furnished milk to young guinea pigs, and certain stages of development were omitted in the accelerated growth phenomena. The histological findings in the implanted ovaries of this feminized male were similar to those shown in Fig. 35, *a*; the ovary, with its great mass of obliterated follicles and its abundant production of lutein cells corresponded to that of a pregnant animal. The following table shows the alterations in length measurements of mature guinea pigs which were produced by such transformations of sex.

TABLE XIII.

(STEINACH).

To Accompany Figure 36a.

Guinea-pig	Weight gm	Distance between ears mm	Distance between the zygomatic bones mm	Length of the head mm
Normal female	845	22	40	74
Normal male	1002	31	43	81
Masculinized female	1200	33	48	87
To Accompany Figure 36b.				
Normal male	980	30	43	80
Normal female	808	21	40	72
Feminized male	516	19	36	67

Sand also obtained the same results in transplantation experiments by which he produced a transformation of sex characters. Lipschütz deduced from the transformation of the clitoris of masculinized rats into a penis-like organ, formed from the two corpora cavernosa, "coming together like the two halves of a gable roof," that the normal inhibitory influences of the ovarian secretion upon the genital eminences had been replaced by the stimulating action of the male hormone; this had given rise to new tissue building, resulting among other things in an enlarged penis-like clitoris. (Compare Hertwig's table, page 188). Finally, there are the observations already referred to which Brandes made on the feminization and masculinization of deer. (Lipschütz.) Antler formation did not take place in feminized males, but in the masculinized females the larynx became like the male larynx. Goodale and Pezard obtained similar results by grafting ovaries into the peritoneal cavity of 24 day, castrated male ducks and chickens. In six weeks their plumage and spurs resembled those of their sisters of the same age.

7. *Hermaphroditism*

In the preceding chapter we saw that there is unequivocal proof, that the sexual characters of the body are influenced by the incretions of the germ glands. But whether this correlation is already existent in the embryonic stage is a matter more difficult to decide. Attempts have often been made by which the presence in one human being of both male and female characters so pronounced

as to constitute hermaphroditism could be explained by assuming the co-existence in one individual of male and female germ glands with incretions acting successively upon the somatic cells in one or the other direction, causing now a development of male, now of female structures, or vice versa. But, except for the bisexual organs found in a few cases of true hermaphroditism, support of this hypothesis is still lacking.

Steinach's experiments have led him to assume the existence of an antagonism between ovaries and testes; he never succeeded in making successful implantation of testicles in castrated female guinea pigs, for soon after the operation the grafted glands would completely degenerate and be replaced by connective tissue. Matsuayma observed an analogous antagonism in his experiments with male and female rats which were united by an anastomosis between the two circulatory systems; when the female was pregnant the testes of the male partner degenerated. In castrated animals, however, germ glands of either sex gradually took root, and the subsequent histological examination showed hypertrophy of the interstitial tissue such as has previously been described. The female gland graft was the more successful one; the ovarian influence on feminized males could be traced for more than three and a half years, whereas the effect of the grafted testicle ceased earlier, and masculinized females returned sooner to the castrated type.

Better results, but only in 20 percent of the attempts, were obtained by implanting bits of both germ glands beneath the skin, or into scarified muscles. If the pieces

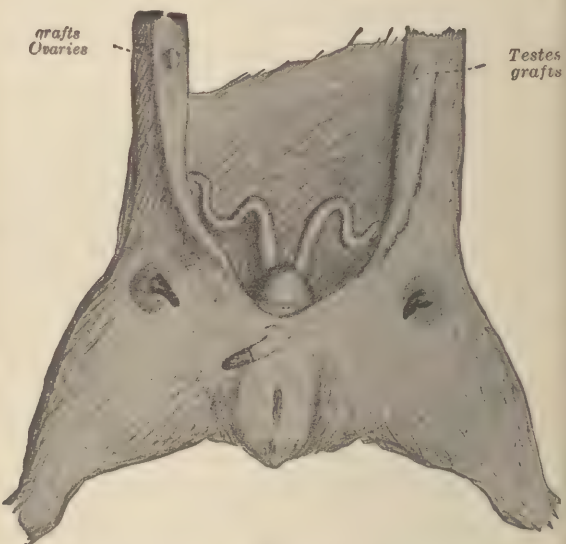
were grafted close together sections of the graft obtained later showed an intergrowth of the cells of one sex gland into the other gland, with areas of degeneration of one or the other type of cells. Sand succeeded still better by transplanting young ovaries into the testes of guinea pigs 5 to 12 weeks old. These ovariotestes continued to grow, and both eggs and spermatozoa were formed; the resultant hermaphrodites showed the characters of both sexes. A male rat, into whose testes ovaries had been engrafted at the age of one month, had at four months a penis 0.6 centimeters long, somewhat smaller than that of the control; both seminal vesicles were developed and contained semen; their length was 0.3 centimeters, the normal length 0.4 centimeters; the nipples of the mammary glands were large, turgid and pigmented; the areolae broad; on pressure these udders gave down normal milk. Accessory genital structures of both male and female were, therefore, markedly developed in one individual. In guinea pigs, also, Moore found an antagonism between the male and female incretions when he engrafted animals with germ glands after uni-lateral castration, but in rats his grafts into unilateral castrates succeeded. He has, consequently, declared himself against the belief in a general antagonism between male and female germ glands. He does not, however, go so far as Witschli, who, on the basis of literary records, denies altogether a morphogenetic dependence of the secondary sexual characteristics upon the incretions of the germ glands. Steinach's conception of an antagonism between ovary and testis also receives

support from the investigations of Harms who found that implantation of testes inhibited the egg cell development in the organ of Bidder, and that such inhibition through the testicle was prevented by injections of corpus luteum and placental lipoids (Stein and Hermann, Fellner).

Many cases of human hermaphroditism are recorded in literature. Neugebauer collected 1,632 cases published before 1906; he had, besides, himself observed and described in great detail a large number of cases. A comprehensive picture of hermaphroditism which has been described by Sands is illustrated in the guinea pig hermaphrodite shown in Fig. 37, *b*. The human hermaphrodite, represented in Fig. 37, *a,* has the outward appearance of a woman; large pendulous breasts; absence of hair on the trunk and limbs; and the feminine distribution of hair in the pubic region. Reared as a girl, this subject applied to a surgeon soon after marriage concerning her abnormal external genitals. Examination showed a penis 6 centimeters long (9 centimeters when erected) with a prepuce 7 centimeters in circumference. In the region of the scrotum there were two pendulous folds of skin containing two well-developed testes, which unfortunately were not examined microscopically. These two scrotum halves corresponded to Hertwig's genital ridges. Lifted up, the penis showed that it was not closed below, but had a cleft representing the groove on the under surface of the genital eminence. On both sides hung rudimentary folds of skin, the germinal folds not having been transformed into a pars cavernosum

urethræ. The penis with its cleft, erectile bodies resembled the transformed clitoris of a masculinized guinea pig.

a



b

Fig. 37. *a*. Hermaphrodite (Reitzenstein; Collection of M. Hirschfeld). *b*. Male guinea pig; castrated at 3 weeks and grafted with ovaries and testes. Drawings made 3 months later. Penis and seminal vesicles developed; mammary glands turgid with broad, pigmented nipples and milk secretion. (Sand.)

This case of Reitzenstein's (Fig. 37, *a*) would, according to the ordinary nomenclature, be designated *hermaphroditus spurius*, the name *hermaphroditus verus* being reserved for cases where both male and female

germ glands are present. Such cases of both ovaries and testes in one person have recently been described by Keussler and others. A better classification of the two forms is that made by Stieve, who divides these conditions into complete and incomplete hermaphroditism.

If we seek to explain them on the basis of the internal secretions we may accept Steinach's view, that a combination of both male and female gland elements has been active in such cases. As evidence, we may point to his artificial hermaphrodites; for example, to his young male guinea pig hermaphrodite, in which the dominance of the female implant checked the growth of the penis, while the nipples and milk cells continued to develop as in a mature female. If after the atrophy of the first testicular graft another was implanted, the incretory effect of the second testes was soon evident; the penis renewed its suspended growth, and acquired the normal male form. The development of the copulative organs is completed during the fourth month, at a time when the specifically masculine growth of the skeleton becomes marked. If at this time the second implant atrophies, and the interstitial cells of the ovary again gain the ascendancy, the skeletal development will be inhibited, and the resulting hermaphrodite will have a feminine body form and female mammary glands, and, in addition, the penis and accessory genital glands of a male.

We may, however, hesitate to accept an explanation of hermaphroditism which limits its origin exclusively to an altered secretion of the germ glands, and yet refuse to

adopt the directly opposite view which completely denies to the internal secretions all influence in the production of these secondary sexual characteristics, and attributes these anomalies to a "developmental tendency" fixed on certain bodily organs at the moment of fertilization.

In the genesis of hermaphroditism there has, I think, too exclusive a rôle been assigned to the germ glands. In one of my own cases of *hermaphroditism masculinus* (clitoris hypertrophy) I observed in a newborn child with well-developed uterus and ovaries an immensely large epoophoron (Wolffian body) and hypertrophy of the two suprarenals, each of the latter weighing 12 grams. This case may be regarded as belonging in the same category with many similar cases in which tumors of the suprarenal cortex in women are associated with masculine sex characters (clitoris hypertrophy and male-like hair growth). Records of such cases have been collected by Knud Krabbe, and these serve as an emphatic reminder that the modification which may occur in each and all of the internal secretions should be considered as possible factors in the anomalies of sexual development. Looked at from this standpoint, the case of Reitzenstein (Fig. 37, *a*) with cryptorchoid testicles may be interpreted as one of inhibited masculine development due to lack of the testicular incretion; and the excess of fat and the underdevelopment of hair in that case may be attributed to hypo-functioning of the suprarenals, and to an altered function of the hypophysis.

It is of subsidiary importance for our understanding of the influence of the internal secretions upon the pro-

duction of morphological sex differences whether we accept Halban's hypothesis that the formation of the genitals is independent of the germ glands; that male, female and hermaphrodite anlages are predetermined in the egg; and that incretions produced by the germ glands serve the development of the respective anlages only as "protective stimuli"; or whether we agree with the Tandler-Grosz hypothesis which assumes that the non-specific soma cells produce the specific sexual form and size of the body only through the action of the germ gland incretions. In either case we allot to the germ gland incretions a decisive influence. But we must not forget that a marked influence upon the production of the sexual form is exercised by other endocrine glands. In particular, the endocrine equilibrium may be disordered at certain points by changes in the functions of the thyroid, the suprarenals, or the hypophysis—changes which may cause an underdevelopment of the germ glands or a hyperfunctioning of other glands. Through such disordered functioning an organism may be produced which constitues a mixture of genuine male and female forms, even though the germ glands themselves have unquestionably developed normally.

Human testicles of an apparently normal male type have been found to contain Graafian follicles and corpora lutea. Pick and Polana and also Salén have described preparations of such bisexual human glands (Fig. 38), and Steinach has found such an "ovotestis" in an homosexual goat (Fig. 39). Similar findings have been described by Prange and Krediet in homosexual goats.

Salén's preparation (Fig. 38) was obtained from a 43-year-old hermaphrodite who was brought up as a girl. She had a clitoris 5 centimeters long, very large labia, a vagina 8 centimeters long, and two egg-shaped bisexual glands as large as hazel nuts. The right half of the figure shows the atrophied seminal canals without spermatozoa and with highly developed cords of interstitial cells; the left half contains one atresic and two empty

FIG. 38. Germ gland of a human hermaphrodite (Ovotestis). *o*, Ovarian portion; *fc*, follicles; *cl*, corpus luteum; *h*, testicle portion; *hk*, seminal canal. (Salén.)

follicles. The bisexual gland (Fig. 39) from a homosexual goat is not, like the human bisexual gland (Fig. 38), composed of two different halves, but the male and female gland tissues are intermingled throughout the organ. The male tissue is similar to that found in cryptorchism, degenerated seminal canals and hypertrophied interstitial tissue; the female tissue contains both ripe and atresic follicles.

At this point the antagonism between the ovaries and the suprarenal may again be recalled. It is known that tumors of the suprarenal cortex in women are associated with hypertrophy of the uterus, absence of menstruation, and a masculine type of hair growth; that is to say, phenomena similar to those which are produced in elderly masculinized guinea pigs. In young girls disease of the

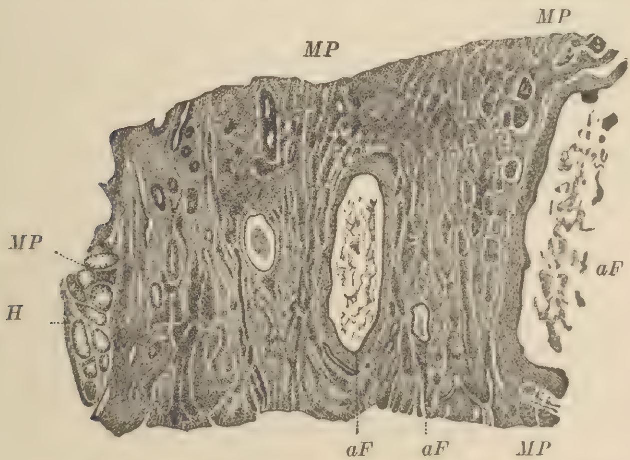


Fig. 39. Section through the ovotestis of a homosexual goat. *H*, testicle tissue resembling that of a cryptorchic testis; *MP*, male interstitial tissue; *aF*, follicles completely and partially atresic. (Steinach.)

suprarenals causes acceleration in the growth of the genitals, thus demonstrating the supremacy obtained by the ovaries in disease of the suprarenals. The opposite conditions are found in old women in whom atrophy of the ovaries is accompanied by a supremacy of the adrenals, the result being an acceleration of hair growth in various parts of the body.

A survey of the findings described in this book will

show us that the thyroid and the germ glands have the greatest influence on body growth and body form. The thyroid is, so to speak, a transformer, acted on by the forces of the outside world and, in accordance with the outside temperature, either accelerating or inhibiting the other endocrine glands and the general cell metabolism. The germ glands determine the form of both sexes; from the neutral anlages the originally indifferent form is molded into male and female bodies, through acceleration or retardation in growth of the respective reproductive organs.

This conception of the origin of sexual characters is in conflict with the theories which assume that the formation of the genitals takes place independently of the germ glands, and that the male, female and hermaphrodite anlages are preformed in the egg. According to this theory, of which Halban is the especial protagonist, the germ gland incretions serve only to develop the given anlages, through "protective stimulation."

The arbitrary transformation of sex accomplished by transplantations of foreign gonads into castrated animals, the production of artificial hermaphrodites possessing varying quantities of male and female characters, proportional to the amount of male and female tissue included in the graft, and, finally, the discovery of natural ovotestes in hermaphrodites demonstrate most emphatically that the sex form is not a fixed entity, determined once for all through fertilization, but that it *is* dependent upon the action of the germ glands. We may, therefore, reassert as an established principle, the thesis

which affirms: "Without the germ gland there would be no specific sex form."

It may also be asked whether both germ gland anlages are present in the ovum, one being stimulated to growth, the other being rendered latent by fertilization; or whether the indifferent egg cell is stimulated to form the specific germinal epithelium of a male or female, according as the egg is fertilized by a spermatozoon bearing an unpaired chromosome or by one bearing only paired chromosomes. The many examples of hermaphroditism of all sorts in both man and beast, the existence of ovaries and testes in the same body, and of ovarian and testicular tissue combined into one anatomical unit, favor the assumption that both germ gland anlages are present in every egg. Assuming the presence in the egg of both sex anlages all these phenomena may be explained as due to an attenuation of the sex-determining action of the fertilizing spermatozoon.

CHAPTER VIII

REPRODUCTION

In describing the histological structure of the ovary (p. 47) we designated as its incretory portion all the disintegrating follicles and all the Graafian follicles which are transformed into corpora lutea. We also assumed that the different varieties of cells composing these follicles, the thecca cells and the lutein cells, constitute the source of origin of the ovarian hormone. Up to now we have made no distinction between the different stages and gradations of the Graafian follicles, but have used the terms female interstitial cells or puberty gland as a general designation.

But the numerous tasks which the ovarian incretion has to perform strongly suggests that this incretion may consist of a number of hormones, produced perhaps by different varieties of cells; for, besides their function of determining bodily form, the ovaries also control the menstrual function, and they initiate placenta formation at the beginning of pregnancy. Evidence of these specific functions is seen in the absence of menstruation after removal of the ovaries, and in the failure of the embryo to fix itself in the uterine mucous membrane if the ovaries are removed within six days following impregnation. Inspired by Born's theory, Fraenkel has sought to fur-

nish experimental proof that these ovarian functions are exercised by the corpus luteum only; he was able to show that not only by bilateral castration, but by burning out of the corpora lutea could the development of the embryo be prevented. Loeb afterward showed that the introduction of a foreign body into the uterus produces in its mucous membrane decidua-like neoplasms, but only if a fully developed corpus luteum is present in one or the other ovary. It is also supposed that the corpus luteum which is developed after the rupture of a Graafian follicle initiates and maintains the monthly hemorrhages of the uterine mucosa, and that from puberty until the menopause the uterus receives these monthly stimuli coming from a hormone formed in the corpus luteum.

Investigations made by Bouin and Ancel have given substantial support to this theory. They mated a virgin rabbit to a buck whose seminal ducts had been ligated. In spite of the fact that no impregnation occurred, changes took place in the uterus and the mammary glands resembling those that occur in a pregnant female; at the same time numerous corpora lutea were also formed. The rabbit is among those animals in which a corpus luteum is formed only during pregnancy or after such a sterile coitus. These changes in the uterine mucosa and mammary glands could also be produced at will by rupturing ripe Graafian follicles, after which follicles even in the untouched ovary would burst spontaneously and form corpora lutea which would induce uterine hyperæmia, hypertrophy of the uterine mucosa, and a simultaneous swelling of the breasts. Burning out of all

the yellow bodies or cutting out of all visible follicles inhibited these pregnancy phenomena, just as burning out the corpora lutea in Fraenkel's experiments terminated actual pregnancies. Many different investigators are agreed that the onset of menstruation coincides with the maximal development of a corpus luteum, reached ten days after the rupture of a Graafian follicle, an indication that the corpus luteum furnishes the stimulus to uterine hemorrhage.

How uncertain we still are concerning the exact relationship between menstruation and the specific action of the corpus luteum is shown by the directly opposed views which are held by other authors who attribute to the corpus luteum an inhibiting effect upon the production of periodic uterine hemorrhages. As proof of this the fact is brought forward, that menstruation has been known to occur two to four days after the removal of an ovary containing a corpus luteum, whether or not the flow was due to begin at that time (Halban and Koehler); the formation of a corpus luteum in lower animals just after the period of heat also sustains the belief in its inhibitory action (Ochoterena and Ramirez); a fact long known to animal breeders, that in cows which fail to develop heat within a normal period heat may be brought on by rupturing an encysted corpus luteum through the rectum, still further confirms the belief of an inhibiting influence of the corpus luteum on menstruation. The results of transplantation experiments also refute Fraenkel's theory; when ovaries are grafted into a castrated female guinea pig, development of the

uterus and enlargement of the mammary glands sets in like in an animal in heat, even when microscopic examination had failed to show corpora lutea and nothing but fresh or disintegrated follicles were ever encountered.

Attempts have been made to solve this question by experiments with extracts of human whole ovary and extracts of isolated corpus luteum. But here, too, the results of different workers are contradictory, probably because of the different methods used in obtaining extracts employed in the experiments; differently prepared extracts may act differently. Two preparations having opposite actions may, indeed, be isolated from a single ovary; one which inhibits bleeding (luteolipoid, Seitz, Wurtz and Fingerhut), and one (lipamin) which promotes bleeding by engendering hyperæmia.

The earlier attempts to exclude the formation of follicles by means of the X-rays also led to contradictory findings. Not until Steinach and Holzknecht had shown the necessity for exact dosage in X-ray application, and that a long interval must elapse after radiation before its effects become apparent in the histological structure, was it possible to prove that ovaries engrafted after disintegration of their follicles and marked increase of their interstitial elements had been produced could bring about the same uterine and milk gland changes as normal ones.

If we wish to view all these contrary findings from a standpoint which will coördinate them all in a way that may explain the correlation between ovary, uterine hypertrophy and placenta formation, we may very well take the middle ground held by Lipschütz. According to his

view the human corpus luteum of menstruation, the corpus luteum of pregnancy and the disintegrating follicle, different objects though they be, produce one and the same incretory substance, being all mixtures of thecca and granulosa cells; their morphological differences are due to the time and the circumstances of their development; rupture of a Graafian follicle is followed by a corpus luteum menstruationis, which, if a fruitful impregnation takes place, undergoes enlargement through cell division and persists for some months to form the corpus luteum graviditatis, and this is replaced during the second half of pregnancy by a corpus luteum that is represented by a mass of disintegrated follicles. Similarity in histological composition is held to produce similarity in incretory action, and by this conception we may harmonize the apparently discordant facts that absence of menstruation occurs after destruction of the corpora lutea, and that heat manifestations corresponding to menstruation appear in animals grafted with ovaries in which there is an increased follicle atresia.

It is thought by Bouin and Ancel, that the activating influence of the ovary on *milk production* is reinforced by the action of a placental hormone which controls the *enlargement of the mammary glands* during the last half of pregnancy. In artificial placentæ induced by incisions made in the uterine wall of rabbits in which a sterile coitus had caused corpora lutea to be formed, these workers found, twenty days later, gland-like collections of cells, such as they had previously observed in placentæ of normally pregnant rabbits during the second half of

pregnancy. With the formation of these glandular masses, milk secretion also set in in their experimental animals. They reasoned from this that milk production fell into two stages—first, a stage of increased mammary gland tissue under the influence of the corpora lutea, and second, a stage of increased secretory activity induced by the hormone of a *myometrial endocrine gland.*

It is difficult to test this theory by transplantation experiments, inasmuch as gravid-like changes of the uterine mucosa occur in these animals before the milk secretion begins. Moreover, Steinach's results in feminization experiments are opposed to the assumption of placental gland tissue which especially furthers milk secretion, since his feminized males produced at times such an abundant secretion of milk that they suckled young animals. Neither is direct evidence of a connection existing between placenta and milk glands which seems to be furnished by the galactogenic effect of injected placental extract, an invulnerable proof, since injections of various other organ extracts produce the same results (Biedl).

We have more than once pointed out that during pregnancy and menstruation, that is, during heightened incretory activity of the ovaries (not as Englehorn assumes during their inhibited activity, through corpora lutea formation, since by the atresia of follicles occurring in the pregnant ovary, there is an increased production of incretory tissue), the thyroid becomes visibly enlarged, its follicles more turgid, and its follicular epithelium thickened. Associated with this increased functional activity of the thyroid there is an increase in the general

metabolism commensurate with the combined needs of both mother and child. Part of the picture representing the general increase in glandular activity during this period is furnished by the enlargement of the adrenals; in consequence of their heightened activity there is increased hair growth and skin pigmentation. We may also mention here the experiments by which Haberland rendered rabbits sterile for three months by grafting them with ovaries from pregnant animals.

Regulation of the events of pregnancy is not confined to implantation of the ovum and provision for fetal nourishment through the formation of a placenta and the production of increased metabolism; it includes also the process of labor. This is influenced essentially by one endocrine gland, the pituitary. Toward the end of pregnancy the anterior lobe of this organ may be increased to as much as two and a half times its ordinary size, and its deeply-staining chief cells show rapid multiplication and other structural changes which have led to their being named *pregnancy cells*. Extracts of this part of the gland, and also of the middle and posterior lobes, have a specific influence on contractions of a surviving virgin uterus. When a young guinea pig uterus is suspended in Ringer's solution at body temperature, weak contractions may be observed to occur regularly; but if a small quantity of pituitary extract, or of the preparations derived from this gland (hypophysin, pituitrin, etc.), be added to the solution, a strong tetanic contraction lasting for some minutes sets in; if the amount of the added pituitary substance be small, this tetanic state is soon

followed by a return to the rhythmic contractions (Fig. 40); larger amounts of the pituitary substance increase both the force and the time of the smooth muscle contractions. Upon the human uterus, pituitary extracts act in the same manner; and if uterine contractions are weak during labor, preparations of the gland may constitute a valuable auxiliary, when administered so that their opti-

FIG. 40. **Contraction curves produced by a guinea pig uterus in 100 cc. of Ringer's solution.** At H $\frac{1}{10}$ mg. hypophysin was added; at P $\frac{1}{10}$ mg. pilocarpin hydrochloride; at A 1/100 mg. atropin sulphate. **Time-markings represent minutes.** (Fühner.)

mum effect will coincide with the time of delivery. Upon a surviving uterus of the rabbit and certain other species pituitary preparations have the opposite effect, and in large doses they bring about a complete arrest of uterine contractions.

The maternal incretions may pass into the fœtus by way of the placental circulation, provided that they are able to permeate the cell layers in the placenta separating

the maternal from the embryonic bloods. The constitution of fetal serum, and its rotation coefficient of polarized light, show that the embryo has its own metabolism, and that it takes over from the mother only the simpler building stones of the foodstuffs. The endocrine glands of the embryo give early evidence of their own functioning; iodine is found in the thyroid during the last months of embryonic life; and adrenalin can be shown in the eighth week, at the time that an enlargement of the suprarenal zona glomerulosa begins. Removal of the parathyroid glands from pregnant rats is said to produce an increased nervous irritability in their young, and to cause these to react with increased violence to the removal of their own parathyroid glands; they die in tetanic convulsions within a few hours after operation. Similar accounts are given of children born to women with parathyroid disease.

The uterine changes resembling menstrual phenomena seen in new-born girls, and the mammary gland swelling in both sexes, accompanied sometimes by an excretion of colostrum-like milk (witches milk), are phenomena attributed to the action of the maternal ovarian incretion; Halban, however, believes these to be post-natal effects of placental materials, especially constituents of the chorion epithelium.

Thyroid disease in the mother may also be transmitted to the child. A bitch with an hypertrophied thyroid gave birth to puppies with enlarged thyroids which, as growth of the animals progressed, underwent regression. When examined later these glands showed no deviation from

the histological picture of a normal thyroid (Carlson). Abderhalden suggests that many congenital deformities may be the result of altered maternal incretions which pass through the placenta to the child.

CHAPTER IX

THE SEXUAL IMPULSE

1. *Germ Glands and Exogenous Influences.*

No better illustration could be given of the change that has lately taken place in our conceptions of coördination than to contrast the explanation according to which the events of conception, pregnancy and parturition were carried out by the brain, which was Pflüger's well-known and widely accepted hypothesis, with the subsequent proofs obtained by Goltz that heat, pregnancy and labor can take place normally in an animal of which the lumbar spinal cord has been completely severed from the brain, and in which all central nervous control of reproduction has, consequently, been eliminated—proofs to which there has more recently been added Fraenkel's demonstration of the rôle played by the corpus luteum in reproductive processes.

In the last third of the nineteenth century physiologists were teaching that menstruation, implantation of the ovum and placenta formation were controlled by specific stimuli going from brain centers to the uterus and the ovary along efferent conduction paths, and that trophic impulses altering their metabolism were transmitted to these organs from the brain. But as early as 1874 Goltz and Freusberg had shown that after complete cross

section of the lumbar cord heat and pregnancy occurred in a dog that later gave birth to one young and two dead puppies. In 1901 Fraenkel showed that removal of the ovaries prevented implantation of the ovum, thereby adding further proof that the internal secretion of the ovary, and not the nervous system, is the actual controller of this function, and that in the act of implantation the brain and the ovarian incretion are completely independent of one another. Investigation brought further advances, and the old theory of Pflüger has been replaced by another of quite a different character, based upon proof that the germ glands send specific stimuli to the nerve centers through the blood—stimuli which give rise to the manifestations of heat in lower animals and produce the sexual impulse in human beings.

The most ancient records of the effects of castration upon man and domestic animals are unanimous in reporting that removal of the germ glands in early life leads either to complete loss of the sexual impulse, or to an extremely meager development of sexual desire at about the time of puberty. It has also been long known that when castration is done after maturity the sexual impulse may persist for a time. Recent statistics show that in 80 percent of such cases the persistence is not longer than a period of two years. In women the cessation of menstruation after castration is accompanied by loss of the sexual impulse. In eunuchoids with congenital atrophy of the germ glands the impulse is also lacking; almost all eunuchoids, physicians report, have never experienced sexual desire.

The connection between internal secretion and heat has been investigated most successfully on frogs by Nussbaum, Steinach, Langhans and Harms. If sexually mature male frogs are castrated no copulatory swelling of the hand occurs at the next mating period, and no clasping reflex is produced by contact with the female; nor can this reflex be elicited by tickling the skin of the sternum or the anterior surface of the thumbs, stimuli that cause clasping motions in normal œstrous frogs. Steinach endeavors to explain this failure of sexual reflexes by assuming that in normal frogs, except during the period of heat, the clasping mechanism is inhibited by special nerve centers which lie in the distal part of the corpora trigemina and the cerebellum, and that at the mating season the incretion from the testes neutralizes the inhibition coming from these places, making it then possible for the clasping reflex to occur. As proof of his conception he brings forward the circumstance that injections of testicular or

FIG. 41. Two cases of eunuchoidism combined with asexualism.

1. Male eunuchoid, 34 years; atrophy of testes. Standing height, 176 cm.; upper body length, 83 cm.; lower body length, 93 cm.; shoulder breadth, 41.5 cm.; hip breadth, 36 cm.

2. Female eunuchoid, 23 years; atrophy of external genitals; vagina blind; uterus and ovaries not palpable; no menstruation. Standing height 175 cm; upper body length, 79 cm.; lower body length 96 cm.; shoulder breadth, 41.5 cm.; hip breadth, 34 cm.

ovarian substance into the dorsal lymph sacs of castrated frogs is followed by feeble manifestations of the clasping reflex, beginning on the following day and lasting for some seven days.

It is a remarkable fact that in frogs castrated several months previous to the breeding season feeble symptoms of heat, and slight clasping reactions, occur at that period. An explanation of this is difficult to give; in accounting for it we might use Semon's hypothesis of inherited or acquired "engrams" and conceive, that certain organic changes produced during previous heat periods had given rise to seasonal sexual "engrams" that induced a recurrence of sexual manifestations when identical external stimuli, such as heat and moisture, were again active. The presence of testicular incretion would, according to this hypothesis, increase this feebly constituted *mnemonic state of irritability*. The assumption of such a protoplasmic memory would also furnish an explanation of the survival of a feeble libido in human beings castrated after maturity. The sexual reactivity produced in castrates by injections of germ gland extract, which sets in several hours after the injection and lasts for some days, may be explained as dependent upon a storing of incretion in the central nervous system and the inauguration of an erotic state when the quantity of stored incretion has reached certain limits. The results of injecting brain and cord extracts of œstrous animals are also in harmony with this hypothesis; for heat manifestations have been produced by injecting such extracts, whereas

with brain and cord extracts derived from castrated animals no such manifestations could be obtained.

Ovarian, like testicular, injections produce similar, though less intense, symptoms of heat. It may be assumed, therefore, that these two glands, the ovary and the testis, contain in their incretions substances that are related to one another, each substance being competent to produce the phenomena of mating.

Lichtenstern and Mühsam have recently obtained unimpeachable evidence of the dependence of the sexual impulse upon the germ glands. During the war Lichtenstern saw many cases of soldiers in whom testicular wounds were followed by complete disappearance of the glandular tissue. These normally virile men soon presented typical pictures of castration—accumulation of fat, loss of hair, change in voice pitch and, most significant of all, complete loss of sexual desire. Into these patients testes of normal men with well-developed interstitial tissue but without spermatogenesis, were grafted upon the scarified musculus obliquus externus. In a short time the eunuch signs began to disappear, the fat was lost, the voice deepened, and normal libido and potency returned. Identical results have been obtained with eunuchoids. At present cures which have lasted five years are known.

Mühsam treated a patient for loss of the sexual impulse produced by tuberculosis of the testicles. Implantation of a sound testicle led to a disappearance of the eunuch characteristics within six months, and at the end of two years normal libido still existed. Lydston de-

scribes cases of eunuchs and eunuchoids, between the ages of 34 and 36, suffering also from hypopituitarism, in whom libido was restored by transplantation of testicles from 16 to 18-year-old normal youths. In one of my own cases I obtained a reawakening of libido and increased power of erection by means of fresh testicle extract, and in other patients greater muscular strength and increased capacity for their occupational tasks were obtained by the same treatment.

A normal loss of sexual libido occurs in men at the age of 50 to 60. At the same period there are signs of ageing in the skin, the skeleton, and the gland functions; there is greater fatigueability, loss of intellectual power, failure of memory, etc.; the atrophy of the thymus and of the thyroid at this period have already been described. Among the signs of ageing as a result of germ gland atrophy must be placed the decrease in the size of the penis and of the accessory genital glands. In women the menopause is associated with cessation of follicle ripening and a fibroid degeneration of the existing follicles. Disturbances of health, which appear in men of 40 to 60, are signs of a male climacteric analogous to the climacteric of women. Such disturbances are headache, fatigue, palpitation of the heart, loss of sleep, psychic depression, etc.; they are manifested histologically by slight pigmentation of the interstitial cells. According to Mendel and Marcuse the more intensive his sexual activity, the earlier man's sexual climacteric appears.

Evidence that atrophy of the germ glands leads to definite symptoms of senility was naturally followed by

attempts to reverse the effects of their ageing by implantation of fresh and active glands from younger animals. Harms describes such an experiment upon a four-year-old male guinea pig. This animal, which had been active and libidinous during the two preceding years, showed a weakening of sexual desire, loss of muscle tone, loss of eye luster, and indifference to its surroundings. After successful transplantation of a piece of testicle from its six-weeks-old son the signs of ageing disappeared in about eight days; the animal became lively; the eyes glistened; the penis became erectile, and spermatogenesis again set in. Placed in the same cage with a female, it immediately began courtship demonstrations, and energetically attacked a rival with characteristic snarling and gritting of teeth, reactions which had been absent before its rejuvenation. The libido remained complete for two months, and then was gradually lost in half a year. Histological examination of the testes during the first period after transplantation showed regeneration of some of the seminiferous tubules and early stages of spermatogenesis; sections examined half a year later showed connective tissue degeneration of the entire parenchyma.

In later investigations Harms reawakened the sexual libido of a 17-year-old dog by means of three successive transplantations of testicle from a young animal, the effect becoming more marked after each transplantation. He also succeeded in producing heat in old bitches by grafts of ovarian tissue, and in one case pregnancy followed. The partial rejuvenation of this animal was ap-

parent, also, in the restoration of her previously defective hair coat.

By following a similar train of thought Steinach devised his method of rejuvenation through an artificial regeneration of the ageing "puberty gland." Basing his expectations upon the results of his masculinization and feminization experiments, he ligated the vas deferens of senile male guinea pigs, seeking to cause hypertrophy of the cells of Leydig through obliteration of the seminal canals. The results obtained justified his theoretical assumptions. Similar operations were made on rabbits by Ancel and Bouin, and on chickens by Massaglia, in both cases with like results. Emaciated animals with defective fur, dim eyes, extinguished libido, indifference to their surroundings, and with atrophied testicles, prostates and seminal vesicles began within eighteen days after ligation of the vasa deferentia to show a reversal of senile changes; there was a return of potency, increased aggressiveness toward other males, renewal of the hair and brightening of the eyes. Autopsy showed that the prostate gland and the seminal vesicles had reincreased to a size normal for young adults, and that they contained secretions; histological examination of the tied off testicles showed a great increase in the previously atrophic interstitial tissue, and disappearance of the seminal canals. When only one vas deferens had been ligated, renewed spermatogenesis and an increase of interstitial tissue were also found in the testicle of the opposite side.

Inspired by Steinach's successful experiments on rats,

and also by his counsel, Lichtenstern performed the Steinach operation on senile men. He reported that there was in almost every case a return of the extinguished libido to "the stormy height of youth," and an increase in muscular power.

The oldest of these experiments date only three years

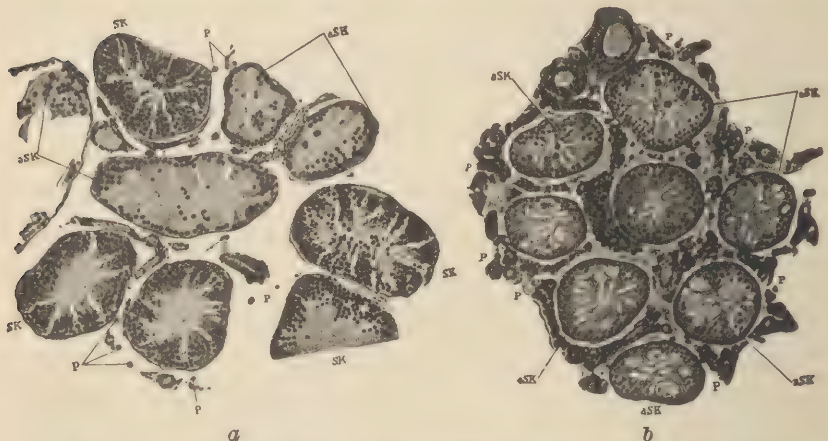


Fig. 42. *a*. Section of testis of old male rat; *aSK*, atrophying seminal canals; *SK*, seminal canals showing beginning degeneration; *P*, detached Leydig cells. *b*. Section through the testis of a brother from the same litter, 5 weeks after ligation of vas deferens. *aSK*, general atrophy of seminal canals which are completely empty up to the cells of Sertoli; *P*, greatly hypertrophied interstitial tissue with an abundance of cells distributed in large chains through the interstices.

back; further investigations must show in how far the other incretory glands are concerned in these regenerating changes of the senile body, and, most important of all, whether, as the opponents of such rejuvenation maintain, such an artificial stimulation of all the life functions may not be followed by a much more rapid decay of the whole rejuvenated organism.

The histological changes produced by ligature of the duct are shown in Fig. 42 (*a* and *b*).

In women DeBruyne succeeded in checking the symptoms of the menopause due to hysterectomy by transplanting pieces of the ovary; the best results were obtained with implantations from the cortex.

Examples of the most varied kinds serve to show the connection between the sexual impulse and the internal secretions. According to Tandler and Grosz, the maximal development of the generative elements in the testes of the hedgehog occurs but once a year, during March to May, and this maximum growth coincides with the animal's period of heat which succeeds its winter sleep.

In autumn the seminal canals atrophy, and simultaneously the interstitial cells begin to increase, thus preparing for the next spermatogenesis and the changes constituting heat (seasonal dimorphism). A similar example of the relation between hibernation and the thyroid has already been mentioned in the chapter on metabolism: where it was shown that thyroid atrophy exists during the hibernating period, and, conversely, that injections of thyroid extract act like a rise in the outside temperature, causing a rapid elevation in the temperature of the hibernating animal, and its consequent awakening. The dependence of the sexual impulse upon such exogenous influences has recently been shown for human beings by Steinach and Kammerer in an exhaustive presentation of experimental and literary data.

The actual age at which the awakening of the libido

occurs in human beings is very difficult to fix exactly. Menstruation fixes the time approximately for the girl, as do also the bodily changes which constitute her secondary sexual characteristics. The dependence of sexual maturity upon climate is shown by many different examples of growth among primitive races in the tropics. The very considerable difference in the height of the man and woman of temperate zones does not exist in the two sexes of the negro peoples of the tropics; there both sexes approximate the same height, and both remain at a relatively immature stage of growth. We have already learned that cessation of growth after puberty is determined by the calcification of the epiphyseal junctions, and that this is controlled by the germ glands and the pituitary body; it is promoted by the action of the germ glands and retarded by the action of the hypophysis. In tropical regions maturity of the germ glands is extraordinarily accelerated; hence, their incretion, rapidly reaching its maximal strength, leads to an early and sudden cessation of growth, which comes to an end almost coincident with puberty. This rapid maturity also prevents the other sexual features which are specific for male and female from becoming so well defined as they become during the slower growth of the body in temperate zones. For this reason men and women of the tropics differ less in the growth and distribution of hair, and in the shape of the face and pelvis, than men and women of temperate zones. The age of beginning menstruation being also dependent upon the rapidity of ovarian development, varies in different climates. A table taken from Steinach and Kam-

merer shows these relationships for different regions of the temperate zone.

TABLE XIV.

Age at Which Menstruation Begins in Different Climates.

Authority	Place	Latitude	Age in Months
Berg	Faroe Islands	62°	194
Frugel	Christiania	60°	202
Kieter, Horwitz	Petrograd	60°	177
Faye	Stockholm	59°	199
Ráven and Levy	Copenhagen	55°	201
Bierre de Boismont	Paris	49°	174
Zaccharias (after Tilt)	Rome	42°	144
Berthérand	Algeria	36°	114
Narbeshuber	South Tunis	34°	132
Rigler	Egypt	30°	114

Race also exerts a definite influence on the age at which menstruation begins. If a group migrates to a climate not greatly different from that of its native land, the time of menstruation undergoes little change, but if migration subjects the emigrant to a temperature greatly different from that of her homeland menstruation is quickly adjusted to the new conditions. European girls brought up in the East Indies menstruate, like Hindu girls, at twelve; in Japan some of the Europeans menstruate even earlier than the natives.

The sexual impulse, like menstruation, appears in the tropics earlier; it also attains, especially in men, greater intensity than in the regions farther from the equator. Correlated with this earlier maturity is an earlier extinc-

tion of the libido and an earlier termination of the child-bearing period, which in some regions, as for instance Abyssinia, is over at the age of twenty.

It would carry us too far afield to consider here all the intricate relationships that exist between the manner of life, kind of food, dwelling, etc., and the fundamental factors of sex upon which these external factors are operative. It suffices to mention as essential observations recorded in these literary compilations that menstruation and the sexual impulse are dependent on climate.

Steinach and Kammerer have demonstrated the mutual relationship existing between the germ glands and the environment by means of experiments on white rats. By breeding them at a temperature ranging from 25 to 40 degrees C., these workers could exhibit the effect of different temperatures on the somatic sexual characteristics and on the sexual trends. Breeding at 36° abolished differences of weight between males and females; the genitals of both sexes developed more rapidly and were larger than those of the controls. Rats reared at high temperatures showed sexual activity at 8 to 10 weeks, and succeeded in copulating a month earlier than rats reared at 15°. At temperatures up to 26° the rats became more prolific, although the number of fertile females was smaller than at lower temperatures (50 percent at 26°, 69 percent at 10°). This smaller number of fertile females was more than compensated by the greater number of rats to the litter born of animals kept at higher temperatures. At 10° the average number of young was 11, at 25° it was 13, at 40° it was again 10.

The testicles of animals reared at high temperatures showed, in microscopic preparations, a greater number of well-filled seminal canaliculi and a better development of interstitial tissue than ordinary testicles show. The average number of Leydig cells in 30 visual fields was 1,060 in the testicles of a rat reared in an unheated cage; in the testicles of 5 rats reared at 36° the numbers were 1,336 to 1,740. The average distribution of Leydig cells, however, was less regular in the testicles of heated rats than in the normal testicle. The number of Leydig cells in different fields varied in the normal rat from 10 to 67; in the heated rats from 11 to 145. In the ovaries of virgin rats reared at 35 it was apparent without counting that the number of interstitial cells was larger than in normal rats, so that in them, also, precocious maturity and premature sexual activity were associated with increased production of incretory tissue.

2. *Inversion of the Sexual Impulse*

Up to now we have spoken of the internal secretions of the germ glands as if the bodies of the two sexes were definitely and distinctly unlike one another; we have assumed for man and for woman a normal type, a specific bodily form which is controlled by its particular germ gland. But in reality this complete man and this complete woman occur but seldom. The characteristics which are typically male and typically female are in their extreme limits represented only in an ideal being, and are never assembled in any one individual; the individuals of each sex always possess a larger or smaller propor-

tion of the characteristics of the other sex. Among other examples illustrating the fact that the body characters ordinarily vary within wide limits, we may recall the variations in the form of hair distribution; the differences in the relative body lengths, and in the shape of the pelvis and of the breasts. We obtain our conception of the male and of the female form from the average of a large number of measurements. The frequent combination of male and female sex characters in one body, added to phenomena observed in hermaphroditism, gave rise to the theory of bisexual anlages in the embryo. This theory, however, we have rejected in favor of the Tandler-Grosz interpretation, which assumes that all sex differences are originally somatic characters which, in the course of development, become modified through the internal secretions of the germ glands. The histological findings in cases of hermaphroditism led us to the assumption that the unfertilized egg contains a bisexual anlage, and that the fertilizing spermatozoon may furnish material which promotes the development of one sex and inhibits the development of the other, or vice versa. Abberations from the anatomical sex form, leading as we have seen to hermaphroditism, complete or partial, have their counterpart in psychical abberations of the sexual impulse, which are expressed in a reversal or a confusion of the object of sexual desire.

Just as little as the sexual characteristics of the body correspond unequivocally to the macroscopic structure of the germ glands, as little does the direction of the sexual

impulse depend absolutely upon its somatic characteristics. In persons with a masculine body and with testes the sexual impulse may be directed toward men, and persons with a feminine body and ovaries may be attracted to women.

Until now, two quite different views have been current in explanation of these phenomena (homosexuality). According to one view, advocated by Schrenk-Notzing and by Kraepelin, homosexualism is a form of degeneration seen in psychopathic persons in whom the still indifferent sexual impulse had become deflected by some strong external stimulus at the time of puberty. The other view, held by Ulrichs, Krafft-Ebbing and Hirschfeld, assumes a *congenitally* reversed tendency of the impulse. In order to be in conformity with the prevailing conception of nervous correlation, a bisexual brain endowment (Näcke) was conceived to coexist with a bisexual body endowment. Just as we now regard somatic sex differentiation as having arisen through the developing of one and the dwarfing of the other gonad anlage, so the direction of the sexual impulse was thought to be determined by developmental changes resulting in the dominance either of a masculine or a feminine brain. Thus homosexuality was thought to arise from a masculine brain in a female body, and vice versa.

According to the conceptions with which we are occupied in this book, the sexual impulse corresponds to the internal secretion of the germ glands; a testicular incretion makes the object of sexual desire woman; an ovarian incretion makes the object of sexual desire man, even

though the testicular incretion be produced in the body of a woman and the ovarian incretion be produced in the body of a man. This view harmonizes with Virchow's often quoted assertion, that "woman is woman precisely through her ovaries." Homosexuality may, consequently, be caused by the presence in one person of male and female gonads, either as separate organs or as combined ovotestes. The relative proportions of male and female germ gland tissues, and the respective times of the separate optimal activities of each gland, will determine the proportionate mixtures of masculine and feminine sexual characters, both of body and mind (Hirschfeld).

Steinach sees in his histological findings evidence in favor of this view. We referred some time since to his description of a homosexual goat with a normal female form and genitals—an animal which developed no signs of heat, but which, like the goats described by Krediet, constantly endeavored to embrace other female members of the flock and rejected all advances of the buck. The macroscopic form of the germ glands in this goat was that of an ovary. In microscopic sections the gland showed a mixture of ovary and testis, with a preponderance of interstitial tissue (Fig. 39). Steinach examined the testes of five homosexual men; all of them showed varying degrees of atrophy of the seminal canaliculi; these were irregularly placed and were separated by connective tissue. The cells of Leydig, however, were not increased in number as is the rule in a cryptorchic testicle; but some of them were atrophied, showing loss of proto-

plasm and beginning vacuolization. Interspersed with these degenerating Leydig cells, he found other cells, distinguished from the interstitial cells by their size, being two or three times larger than ordinary interstitial cells. They were also characterized by their larger quantity of coarsely granular protoplasm, by their large nuclei, often twice or thrice the size of Leydig cell nuclei, and by their small chromatin content. They stained more feebly, and seldom contained crystals, as do the cells of Leydig. Steinach named these structures F cells and he regards them as female cells capable of producing the most different types of homosexuality; either by influencing merely the brain, in which case a psycho-sexual inversion that might be periodic in character would be produced; or by inhibiting the incretion of the male interstitial cells during the period of development, and thereby producing somatic features of a feminine sort. Steinach explains the phenomena of bisexuality, in harmony with these histological findings, as being due to a periodic dominance of the male or female incretion of bisexual germ glands; periods when testicular incretion is dominant are synchronous with times of attraction toward females; periods when the ovarian secretion is dominant are synchronous with times of attraction toward males; the bisexual animal is attracted now to its own, now to the opposite sex. Most of the other workers who have occupied themselves with these matters have been unable to confirm Steinach's results.

Through these findings Lichtenstern and Mühsam were induced to castrate homosexual men and to graft them

with normal testicles. These workers report that within twelve days to six weeks after operation the impulse was reversed to its normal direction, and a regression of the feminine body features took place. Stabel, who kept these cases under observation for a long time, found that eventually the grafted glands degenerated and the homosexual tendency reappeared. A metaplasia of the lutein cells of the ovary was described by Henri Claude in subjects of "formes frustes" of virilism in whom peculiar alterations of personality and psychosexual disturbances had occurred at puberty, and disturbances of menstruation and anomalies of hair distribution had appeared at later periods.

This question as to whether abnormal psychosexual behavior was evidence of inverted internal secretions, I attempted to answer by approaching the problem from another side. The body proportions of a normal man are, as we have already seen, the result of coöperation between the glands which for a long period promote growth (thyroid, hypophysis, thymus) and the glands which from the time of puberty inhibit growth (germ glands). If the influence of the latter is absent, there is produced a body of the type of the eunuchoid with its characteristic proportions of short trunk and long legs. By measurement of 250 homosexuals I found that the ratio of upper and lower body lengths differs considerably from the ratio in heterosexual men, and that it approaches the ratio for the eunuchoid. This anomalous condition was also shown for the total height, the average height of homosexuals being 172 centimeters, whereas Weissen-

berg found 164.8 centimeters the average of 770 height measurements of normal men.

Since the absolute length of the trunk in homosexuals is subnormal its disproportion to the standing height is all the more striking. The sitting height of homosexuals averages 48.5 percent of the standing height; for nor-

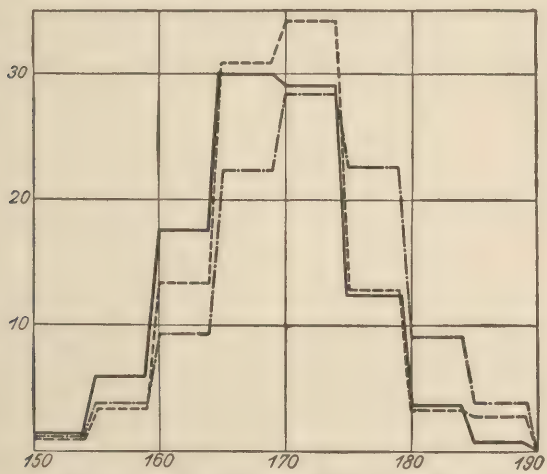


FIG. 43. Graphic representation of difference in measurements of normal and homosexual men. Unbroken line, 770 cases of Weissenberg; -------, 120 heterosexual; —-—-—, 250 homosexual cases of Weil. Body lengths represented in cm. on the abscissa; percentage distribution on the ordinates.

mal men the average is 52.5 percent. The ratio of upper and lower body lengths in homosexuals is 100:108, in normal men 100:105. These variations are represented in the curve shown in Fig. 44. In other words, many homosexual persons, like eunuchoids, show partial infantilism as the result of a belated inhibition of growth

by the germ glands, or a dominance of the growth-promoting glands, the thyroid or hypophysis—an infantilism that may be accompanied by a parallel arrest of

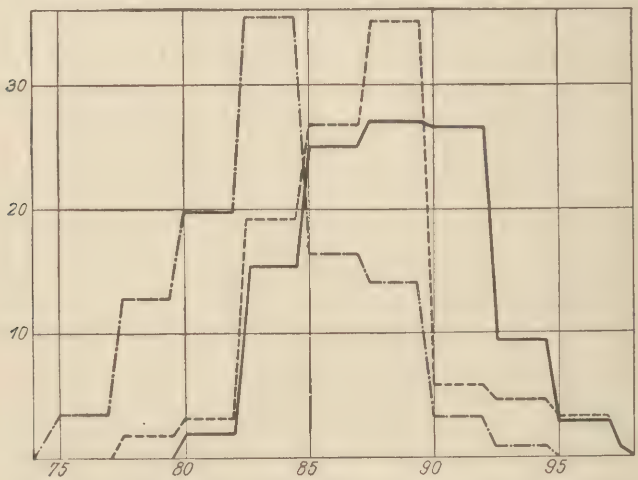


FIG. 44. Graphic representation of differences in the sitting height of normal and homosexual men. Same as Fig. 43.

psychosexual behavior at a juvenile level. This conception accords with the Freudian definition of homosexuality as a physiological stage of puberty.

CHAPTER X.

THE MIND AND THE INTERNAL SECRETIONS

That the sexual instinct is connected with the internal secretions is a belief firmly established by the results of transplantation experiments and by observations on eunuchoidism and other related conditions. This connection being admitted, the relationship with the internal secretions is naturally extended to include all the instincts, "the basic psychic phenomena from which all intellectual development proceeds" (Wundt). This conception once achieved, we are tempted to take the next step and to conclude, that the higher mental activities also depend upon the endocrine glands. It is not an absolute necessity to take the standpoint of the radical materialist, a standpoint from which everything psychical is regarded as an effect or a property of organized matter; it is possible to adopt the conception of a psycho-physical parallelism, which postulates "that psychical events are regularly accompanied by definite physical phenomena and that between the internal and external life processes definite causal relationships exist." Such relationships need not be rejected, *a priori*, as chimerical.

These innate mutual relationships between temperament and bodily constitution become, according to F. S. Hammet, more sharply defined with the increased influ-

ence exerted by the central nervous system upon specific organs in the course of their development. In the incretions of the endocrine glands, which in lower animal forms are provided with ducts connecting them with the alimentary canal, and which have in part excretory functions, we have the best example of how through the creation of new internal stimuli reciprocal activities may be multiplied.

Hammett defines temperament as the total expression of instinctive behaviour produced by the influence of internal stimuli; among these stimuli metabolism of the endocrine glands plays a striking part. Bodily constitution and temperament stand toward one another in the relation of a reversible reaction which may be expressed by the formula: Bodily Constitution $\rightleftarrows$ Temperament. The total metabolism varies with temperament, being relatively uniform in persons of a phlegmatic nature, and variable in those of a nervous temperament. The total metabolism also shows a parallel variability in respect to nervous irritability, and the functional activity of the endocrine glands is likewise parallel with variations in the total metabolism. (Other examples of such interactions are given in the last chapter.)

Are the intellectual differences between men and women also parallel to differences in their germ glands? Is it for this reason that "Woman is woman precisely through her ovaries?" In attempting to answer this question we may be in danger of leaving the safe ground of facts established by experiment and observation, and of wandering into the region of philosophical speculation.

However, it is a fact that during the past two decades experimental psychology has accumulated a rich supply of material which suffices to reveal mental differences existing in the two sexes in regard to many matters concerning which measurable differences in response to stimuli could be determined. It has been found, for example, that men distinguish sound and pitch better than women. Among older school children boys excel girls in mathematics, in critical and logical handling of formal problems, in gymnastic exercises. The color sense is better developed in women, and school girls excel school boys in memory and in ability to perform delicate handwork. The mental life of man is more occupied with abstract considerations, and with creative activities. Woman is more concrete, and has more shades of feeling; she is more suggestible, and her interests are personal; her fantasy is permitted freer play (Wreschner, Thompson, Giese, Lipman and others). Even if, with Thompson, many differences be attributed to cultural influences, educational methods, and suggestions from the environment, there still remain certain differences not to be explained by these factors.

In this place may be mentioned such familiar phenomena as the changes in the psyche produced by castration; loss of initiative, indifference to surroundings, fatigueability; also the alterations in affectivity during pregnancy, with its frequent moodiness, hypersensitivity to tastes and smells, depressive and hypomanic changes in the emotions; and, finally, the psychic disorders of men-

struation and of the menopause—pathological states which nevertheless display the physiological influence of the internal secretions on the psyche, since they can be overcome by gland transplantation and by glandular therapy.

It has long been known of endocrine glands other than the sex glands that their functional activities involve alterations of the psychical state. In 1791 Schreyer sought to explain the action of the thyroid on the brain by assuming that through its rich vascular supply the thyroid served as a blood reservoir for the brain, being able to guard it against damage during moments of temporary interference with the carotid circulation, and, on the contrary, to protect it against a sudden oversupply of blood. The gland was, therefore, looked upon as a safety valve, stationed in the path of the blood stream to the brain, and able through the contraction or dilatation of its vessels to send blood to or to receive it from the brain as need occurred, and so to guard it against anemia or hyperemia. But we know, to-day, that increased secretion of the thyroid produces increased irritability of the entire nervous system for all stimuli, whether of central or of peripheral origin. Through this increased irritability we may explain the psychical changes in Basedow's disease. According to Moebius the symptoms "are to be compared with slight drunkenness, consisting of mild maniacal moods easily succeeded by depression." These changing moods correspond to alternate laughing and crying, increased rapidity of thought and flight of

ideas. "The character changes, the patient becomes mistrustful, irritable, moody, strikingly euphoric, often deeply dejected."

Quite different effects are produced by congenital ab-

FIG. 45. Adult cretins. (Kraepelin).

sence of the thyroid or by its hypofunctioning, as in myxoedema. The responsiveness of the nervous system is diminished by loss or inadequacy of the thyroid secretions; there is a characteristic apathy which may lead

to inhibition of the psychic functions, with slow, undecided movements and slow, monotonous speech. In extreme cases the loss of thyroid secretion leads to idiocy, to simple, mindless vegetation; such invalids have been likened by Charcot to hibernating animals. Psychoses such as melancholia, hallucinations, etc., also occur in myxoedema.

The brilliant results obtained through the treatment of myxoedema patients by thyroid preparations or by implanted glands prove that lack of the secretion, and not a general psychopathic condition, is responsible for these psychic modifications. The fact that when the myxoedema disappears and the psychic powers are restored abondonment of thyroid therapy is followed by a relapse is another proof that this condition is due to lack of the thyroid secretion.

The same symptoms which accompany lack of the thyroid gland exist also in another widespread disease not yet fully understood, namely cretinism. In this disease there is a parallel inhibition of bodily and mental growth, the main determinant of which appears to be a simple lack of iodine in the food. Such iodine deficiency apparently acts in the first instance by a disorganization of thyroid metabolism; in the absence of iodine the specific thyroid incretion cannot be manufactured, and a complex of morbid changes results. These changes are morphologic, affecting both the thyroid gland and the entire body, and functional, affecting the psychic and many of the organic functions. Cretinism that is prenatal or acquired in infancy profoundly modifies the whole developmental

history. In the past few years very beneficent large-scale results have been obtained in the amelioration and prevention of this disease by means of simple iodine feeding. The cretins shown in Fig. 45 illustrate the consequences of this disease.

Very striking psychic modifications have been described by Fraenkl-Hochwart in cases of hypophyseal tumor as "hypophyseal mental dispositions": cheerful moods with restful temperament, indifference, contentment, extraordinary euphoria and drowsiness.

Departures from the average mental development have also been described in cases of pineal tumor; in children, acceleration of intellectual as well as bodily development, and especially of sexual functions, have been described. In one such case a six-year-old boy was said to have a mental age of seventeen. Extraordinary intelligence and cheerfulness have been reported in adults (Anton). Attempts have been made to explain such cases of precocious maturity by assuming the existence of a physiological inhibitory influence of the pineal gland upon the germ glands; removal of the normal pineal inhibition, such as might result from disease would, consequently, be followed by sexual precocity with its associated increase in intellectual powers (Hoffstaetter). Other workers, on the contrary, attribute to the pineal gland a direct stimulating influence on the intellect and even endeavor by means of pineal gland preparations to better the intelligence of backward children (Berkeley, Sommer). These contradictions may be explained by the difficulties of operations upon the pineal gland, difficulties which have

so far made it impossible to determine its exact physiological function.

At this time it seems appropriate to refer to the parallelism which Magnus Hirschfeld, Kronfeld and others have pointed out between psychosexual infantilism and constitutional infantilism. In the former, psychosexual infantilism, there is an arrest of the sexual love life, and of sexual desire at the infantile stage; the latter, constitutional infantilism, may be either of a limited type, characterized by a lack of development of the germ glands or of the secondary sexual characteristics, or by persistence of the thymus or other peculiar stigmata; or it may be general, resulting in the persistence of a body having an infantile form and size.

Recognition of parallelisms between psychic disturbances and the anatomical and physiological state of the endocrine glands is constantly increasing. The province of the thyroid psychoses has been well investigated, and repeated endeavors are made to connect dementia praecox with disturbances of the internal secretions, especially with morbidity of the germ glands. Earlier, attempts were made with varying success to cure dementia praecox by extirpation of the germ glands or of the thyroid, but with varying success. Kretschmer has lately pointed out how closely the psychic changes are associated with definite constitutional anomalies and how frequently (in almost half the cases) the asthenic habit so common in eunuchoidism is found in dementia praecox, an observation that has been confirmed by Davis, Kloth, A. Meyer and Sioli.

It seems quite as likely that the disturbances described as "puberty psychoses" are caused by a hyperactivity of the germ glands, at the period when their specific reproductive ripening begins, as that the manifold forms of psychic infantilism are due to their hypoactivity caused by inhibited growth—an assumption which may be regarded as verified.

It would lead us beyond the goal of this book to pursue further the relationships between the psyche and the internal secretions. It must suffice if we have made it evident, that the somatic changes governed by the endocrine glands go parallel with psychical events. It is the task of psychiatry to find further evidences of this relationship and thereby to attain means for the study and treatment of mental diseases.

CHAPTER XI

THE CHEMISTRY OF THE INCRETIONS

The study of the internal secretions has for one of its aims the isolation and synthetic production of the hormones, the greater number of which are, so far, known only by their action. Not much has yet been accomplished in this field; adrenalin and cholin have been produced synthetically; thyroxin, a compound which Kendall has obtained from the thyroid and also constructed synthetically, is, presumably, the thyroid hormone. The active substances of the hypophysis have been partially determined by Fühner; and Hermann believes that he has isolated from an ovarian extract a unit chemical compound that possesses hormone properties.

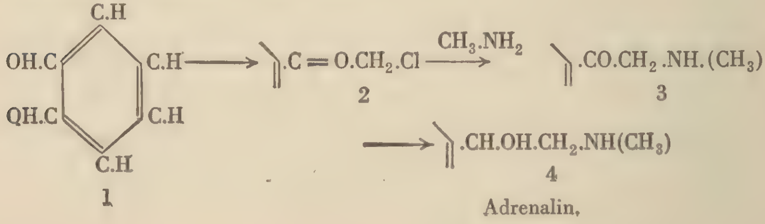
In the fifties of the last century Vulpius and Virchow had already shown that the cells and the intercellular spaces of the suprarenal medulla contained a specific substance. If a cross section of the suprarenal gland be covered with a solution of iron chloride, there appears in the center an intense green color; alkalies and solutions of iodine and chlorine produce a rose to carmine red color. These chemical reactions offer reliable means of detecting adrenalin in dilutions of 1:50,000; for lesser concentrations there are available several methods which depend

on the fact that adrenalin readily oxidizes by attracting the oxygen from oxides. In the presence of manganese dioxide adrenalin is colored red; a one-percent solution of sodium persulphate has the same effect. A mixture of sodium tungstate and phosphoric acid will, according to Folin, give a blue color to adrenalin solutions of 1 : 3,000,000. But none of these colorimetric methods are specific for adrenalin, as similar color reactions are obtained with ammonium bases, amins and other substances. Tests of greater delicacy are the more specific biological reactions (see next chapter). By the aid of biological methods Takamine and Aldrich succeeded independently in obtaining crystals of adrenalin from suprarenal extract. Isolation of adrenalin was possible through the fact that, after the proteins and other precipitable metabolic products are removed from the gland substance by alcohol and acetic acid or its salts, adrenalin is precipitated by ammonia in fine, needle-shaped crystals. After several recrystallizations, solution in acid and reprecipitation with ammonia, a substance is obtained with a constant melting point of 212° C. An important point in explanation of the biological action of adrenalin is that its oxidation and consequent decrease in activity depend upon the reaction of the medium; its activity is accelerated in alkaline media and is optimal at an (OH) concentration of Hp=7.5 to 8.5. In the presence of air, or of proteins, or of nucleo-proteins, its decomposition is accelerated.

The human suprarenal contains about 6 milligrams of adrenalin for every 100 kilos of body weight; in other animal species the content varies within narrow limits of

this amount (Batelli). According to Schmorl and Ingier the adrenalin content in man is 1.52 milligrams, till the 9th year; later it is 2.58 milligrams in males between 11 and 20 years, and 2.20 milligrams in females of the same age. Between 21 and 30 years of age the difference increases, being 4.21 and 2.45 milligrams. These quantities of adrenalin are given up to the blood some twenty times in the course of a day, if conditions are the same in the suprarenals of man and of the cat, for in experiments on the cat it was found that the suprarenals delivered to the blood an amount of adrenalin which would average a proportion of about 5 milligrams a day (Biedl). The figures obtained by different investigators naturally vary, being dependent upon the delicacy of the methods used. But even if the amount of adrenalin were double or more than these estimates indicate, this would still represent an adrenalin concentration in the blood of not more than the ratio of 1 to 500 millions already given.

The steps in the synthetic manufacture of adrenalin are, according to Stoltz, as follows: From chlor-acetyl-chloride and the ortho-dioxy-benzol (brenzcatechin) there is produced the chlor-aceto-compound of divalent phenol (2), which upon treatment with methylamin goes over into the corresponding aminoketone (3), which by reduction becomes adrenalin (4).



The synthesis of adrenalin in the animal body is presumably made from the amino acids, phenylalanin and tyrosin (see page 134). Attempts have been made to show that an increased adrenalin production is obtained by adding phenylalanin, tyrosin, or tryptophan to suprarenal infusions maintained at body temperature. But the increased precipitations obtained by addition of ammonia to the resulting extracts, and also the more delicate color reactions thereby produced, may be attributed to the many different putrefactive bases produced during this process. The dioxyphenylalanin which occurs in plants (in vicia faba, according to Guggenheim) may be transformed into a pigment by oxidizing ferments of animal origin (Bloch). Hence, the increased production of melanin that occurs in the skin in Addison's disease arouses the suspicion that in this disease similar compounds or, perhaps, adrenalin itself may have become transformed into pigment.

Native adrenalin is optically active; it rotates the plane of polarized light to the left (specific rotation coefficient $= -50.72°$). Synthetic adrenalin is optically inactive, but it may be split up into its dextro and levulo rotary components through the difference in solubility of their tartaric acid salts. The pharmacological action of pure dextro-rotary adrenalin is almost zero. This is another interesting example of how exactly the chemical structure of an incretion must be fitted to the substratum in which it is to work—a requirement which we previously saw exemplified in the action of ferments. The biologically active group of the adrenalin molecule is not the benzol

ring, but the side chain, alipatic amins being also able to act on the sympathetic nervous system.

The second suprarenal hormone, cholin, is an amin isolated from the cortex. It is not confined to a single tissue, as is adrenalin to the chromaffine system; it occurs in all the organs, either as a free base or as a building stone of phosphatids. The amount of free cholin in the different organs varies; it is 0.01 percent in the spleen, 0.03 percent in the small intestines, and 0.07 percent in fresh liver. It is best detected by converting it into its nearly insoluble salt of platinum chloride, in which form it has a constant boiling point and characteristic crystals. Solutions up to 0.03 percent give a rose violet color when evaporated with alloxan on a water bath. Heated with alkali, the cholin base can be detected in dilutions of 1:2 million by the characteristic odor of trimethylamine (Kauffmann). Cholin is presumably ingested in the food, since it occurs in plants in amounts of 0.01 to 0.1 percent. In the body, cholin is thought to be transformed into creatin, by a splitting off of two of its methyl groups in the presence of urea, which thereby passes over into cyanamide; and by oxidation of the resultant methylaminoethanol it is transformed into creatin, with methyl glycocoll (sarcosin) as an intermediate product.

This formula represents the decomposition of cholin as Riesser believes it to take place, a process that appears probable from the appearance of creatinine in the urine after feeding with cholin. Opposed to his belief, however, are negative results obtained by Satta, Guggenheim and Löffler. The intermediate steps in cholin metabolism,

therefore, must still be regarded as not definitely known. Serin is looked on as the precursor of cholin in the body.

$$\underset{\text{Cholin}}{\begin{matrix} CH_3 \\ CH_3 \\ CH_3 \end{matrix}\!\!>\underset{\displaystyle |\atop OH}{N}.CH_2.CH_2OH} + \underset{\text{Urea}}{CO\begin{matrix} NH_2 \\ NH_2 \end{matrix}} \longrightarrow [2\ CH_3\ OH] + \underset{\text{Cyanamid}}{CN.NH_2}$$

$$+\underset{\text{Methylaminoethanol}}{CH_3.NH.CH_2.CH_2OH} \xrightarrow{+O_2-H_2O} \underset{\text{Sarcosin}}{CH_3.NH.CH_2.COOH} + CN.NH_2$$

$$\longrightarrow \underset{\text{Creatin.}}{C\begin{matrix} NH_2 \\ =NH \\ -N.(CH_3).CH_2.COOH \end{matrix}}$$

According to Hofmeister the process is a methylization of the intermediary product, oxyethylamin:

$$\underset{\text{Serin}}{\begin{matrix} CH_2OH \\ CHNH_2 \\ COOH \end{matrix}} - CO_2 \longrightarrow \underset{\text{Oxyethylamin}}{\begin{matrix} CH_2OH \\ CH_2.NH_2 \end{matrix}} \longrightarrow \underset{\text{Cholin.}}{\begin{matrix} CH_2OH \\ CH_2.\underset{\displaystyle |\atop OH}{N}.\!\begin{matrix} CH_3 \\ CH_3 \\ CH_3 \end{matrix} \end{matrix}}$$

The artificial synthesis is carried out by addition of trimethylamin to chlorethyl alcohol. (Wurtz.)

$$N(CH_3)_3 + Cl.CH_2.CH_2OH + NH_4OH = \underset{\displaystyle |\atop OH}{N}(CH_3)_3.CH_2.CH_2OH + NH_4Cl$$

The antagonistic effects of cholin and adrenalin on intestinal movements and on blood pressure have already been spoken of. It may also be added that cholin, instilled into the eye, produces contraction of the pupil, while adrenalin causes pupil dilatation. This action of adrenalin, however, is scarcely evident in normal states of health, and becomes conspicuous only when there is increased nervous irritability, as in Basedow's disease.

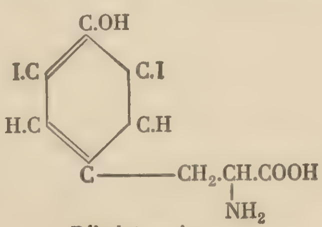
In the suprarenal cortex, cholin is combined with the lipoids that are accumulated there in large quantities; they are visible in the cells as fine granules which are soluble in ether, alcohol and chloroform; are stained black with osmic acid and are intensely colored by such special fat stains as Sudan III. These granules are doubly refractive in transmitted polarized light. Their chemical structure indicates that they are mainly lecithins which, by variations of the fatty acid radical, or by intramolecular transpositions, or by replacement of cholin with other amins may take on a multitude of forms, these forms apparently having a specific structure for each organ. Sphingomyelin, one of the forms assumed in the suprarenals, is a di-amino phosphatid (Rosenheim and Tebb), of which cholin is the amino base; it was named neurin by von Thudicum. Cholesterin and its fatty acid esters are also found with cholin, though they do not serve as sources of it.

The thyroid gland is characterized chemically by its large iodine content; it seemed, therefore, quite logical to consider this element as one of the building stones of the thyroid incretion. The contrary view already spoken of as held by Herzfeld and Klinger, namely, that iodine serves only to activate the incretion, without taking part in its molecular composition, is not sustained by the experimental findings of most investigators. The iodine content, though varying with age, diet and race, is normally about 6.5 milligrams in the whole gland. It is increased during pregnancy, averaging 18.5 milligrams in pregnant and only 17 milligrams in non-pregnant cows.

Reckoned in proportion to the body weight, however, the iodine percentage is the same in both cases (1.8 mg. to 100 pounds). It occurs as an organic compound; ionized iodine is never found except in mere traces.

Baumann was the first to discover iodine in the thyroid, where he found it in the form of a combined protein, thyreoglobulin, which, however, has not a constant iodine content, inasmuch as its iodine percentage can be increased by potassium iodide feeding. The average composition of human thyreoglobulin is C = 51%, H = 6.67%, N = 15.06%, I = 0.154% (Blum and Grützner). After hydrolytic cleavage of thyreoglobulin Baumann obtained, by further decomposition, another iodine compound, iodothyrin, which also varies in its iodine content from 3 to 5 percent.

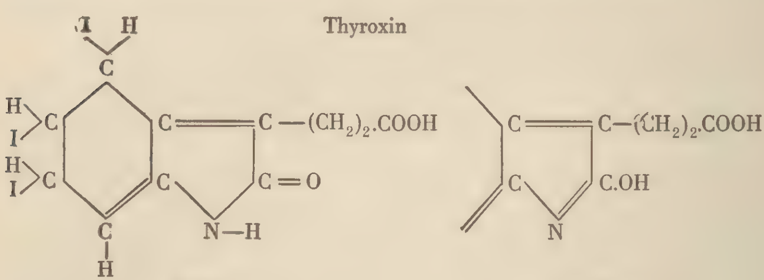
Oswald separated the thyroid proteins into two different groups, one containing iodine, the other containing no iodine, and showing by its phosphorus content a close relationship to the nucleo proteins. The iodine percentage of Oswald's first group is also inconstant, varying within limits of 3 to 6 percent; by further splitting, it yields iodothyrin, the composition of which is not known, and diiodotyrosin, a compound contained in large amounts in the skeleton ash of corals and sponges.



Diiodotyrosin

After hydrolyzing dried and defatted thyroid gland with 5 percent sodium hydroxide, Kendall was able to split off 75 percent of the iodine as a water soluble, dialyzable, organic compound. From this he obtained an acid-soluble, crystalline compound, which contained 60 percent of iodine, and which produced in animals the same physiological effects as thyroid extracts. He called this compound thyroxin and assigned it the structure of a 4.5.6 trihydro-, 4.5.6 triiodo-, 2-oxy- indol propionic acid. Thyroxin occurs in two tautomeric forms, having different positions of the hydroxyl groups; and by taking up of water it becomes converted into a dibasic acid. The structural formula of both forms are given here.

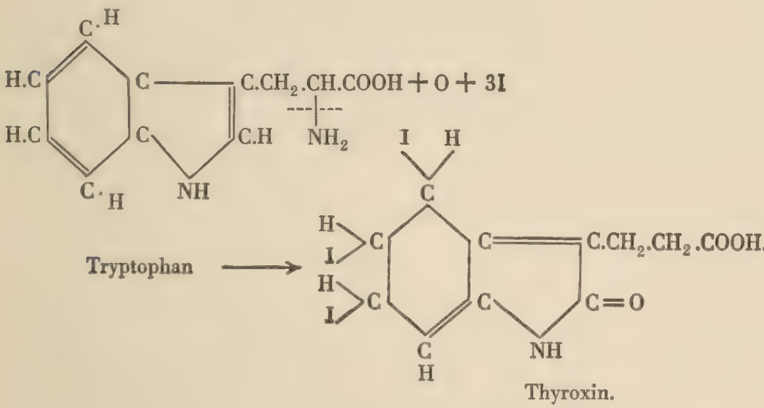
Thyroxin



Ketoform Enolform

Tryptophan (indol-alpha-amino-propionic acid) may be looked upon as the antecedent of thyroxin in the animal body, the conversion of the former into thyroxin being effected by deamidization with reduction of the alpha side chain, oxidation and the addition of iodine. Although it has so far not been possible to deamidize amino acids in this way in infusions of organ extracts, the results obtained with bacteria, yeast, and other fungi

point to the fact that deamidization may take place in the living animal cell: Oxidation and reduction are constantly going on in every cell of the organism, and that the iodine in the thyroid is linked to the benzol nucleus is proved by the increase of thyroxin after feeding with potassium iodide.



Many other facts indicate that the incretion of the thyroid is an iodine-containing compound; for instance, feeding with the iodine fractions of hyrolyzed thyroid proteins accelerates the metamorphosis of tadpoles (Rogoff and Marie). On an iodine free diet, the iodine content of the thyroid remains for a long time constant; from which it may be assumed that by combining the free iodine in the circulating blood with its own substance the thyroid plays a detoxicating rôle; and that at the same time it makes use of the deionized iodine in the construction of its own incretion. The specificity of the iodine-containing thyroxin is proved by experiments; these have shown that its action is equivalent to thyroid

gland feeding, or to injection of thyroid extracts—increasing the metabolism of myxoedematous patients and reducing weight through loss of the body fats and proteins.

Hypophyseal hormones have been isolated by Fühner as crystalline substances, but their molecular structure and chemical composition is not yet known. After removal of proteins the amino bases of hypophysis extracts are precipitated with phospho-tungstic acid. The acid is then removed with barium, and the residue dissolved in sulphuric acid, from which it is evaporated in a vacuum. The resulting crystals are separated by fractional crystallization into four compounds, which give different biological results. The first fraction, which acts on the blood pressure, has no influence on respiration or on the uterus; the second fraction acts on all three of these, blood pressure, respiration and uterus; the third fraction acts more energetically on the blood pressure and uterine contractions; the fourth fraction, contained in the mother liquor, has a slight action on blood pressure and respiration, and no effect on the uterus. The mixture of these four fractions is the "hypophysin," furnished by the trade in 1-percent solutions. Guggenheim maintains that the hypophysis contains only one active hormone, consisting of an ether-like combination of an acyl and an alcanolamine (an amin with one oxy- and one amino group attached to one carbon atom). In his opinion, Fühner's different preparations are only different degrees of purity of the same incretion.

But Leschke has lately obtained results which indicate that hypophysin is a mixture of compounds having dif-

ferent actions. From an hypophysis infusion, he succeeded in precipitating with picric acid and methyl alcohol a polypeptid-like compound which diminished the quantity and raised the concentration of urine in patients with diabetes insipidus, polyuria, and kidney inflammation, as well as in normal subjects. And from alcoholic extracts Crawford precipitated with mercury bichloride a substance of which 0.16 milligrams raised blood pressure in a dog to 66 millimeters of mercury. Leschke also isolated substances with specific action on the heart, blood pressure, and uterus; but these fractions have not been analyzed further. The antidiuretic substance could be obtained only from mixtures of the anterior and middle lobes and not from the posterior lobe.

Robertson is said to have obtained from the hypophysis a growth-regulating substance which he has named tethelin. He found it to contain 1.4 percent of phosphorus, and to possess four nitrogen atoms to one atom of phosphorus. When hydrolyzed it splits off inosite, a hexose containing a symmetrical ring. Fed during long periods to white mice this compound first slows, then accelerates growth. The average length of life was increased 13 percent in male and 11 percent in female mice, a lengthening of life which held good for carcinomatous as well as for normal animals.

Spermin, a compound having the formula $C_5H_{14}N_2$, isolated by Poehl as a phosphorus salt from extract of testes, by precipitating the proteins with phosphotungstic acid, is regarded by him as the hormone of the male germ gland. The specific action on blood pressure, respiration,

and metabolism, which he ascribed to spermin, has not been observed by other workers (Biedl).

From ovarian extracts Iscovesco has obtained, by means of fat solvents, a number of lipoids. In large doses these lipoids act as poisons, having produced paralysis of the extremities in female rabbits. Fellner also extracted from the ovary and the placenta, by means of alcohol and ether, substances which greatly accelerated growth in the genitals of young rabbits into which the extracts were injected.

With these findings as a basis, Hermann sought to isolate the active hormone of the ovary. Dried ovaries were extracted with ether, and from these extracts the greater part of the unsaturated phosphatids were precipitated with acetone; the mother liquor was then freed from cholesterin and its esters by gradual concentration. The remaining syrup was fractioned, distilled in a high vacuum, and that fraction which, at an outer temperature of 240°C. and in a vacuum of 0.06 millimeters of mercury, distilled over at 193° C., leaving behind the last remnants of cholesterin, was then redistilled. The resulting thick, irridescent, yellowish oil was found to be easily soluble in alcohol, petroleum ether, acetone and benzol. It had the composition: $C = 81.33 - 81.62\%$; $H = 11.32 - 11.49\%$, and was a cholesterin derivative. Five subcutaneous injections of this substance, in quantities of 0.04 to 0.06 grams, made into 8 weeks old rabbits, produced in them such a modification of uterus, vagina and tubes that these organs resembled those in a pregnant rabbit. In castrated males, injected with this substance, Hermann de-

scribed mammary gland hypertrophy resembling that seen in feminized males.

From the corpus luteum Wintz isolated two lipoids, luteolipoid and lipamin. The latter acted on the rabbit uterus like Hermann's preparation, and also restored menstruation in cases of amenorrhea.

From calves thymus, Romeis isolated a nucleoprotein by treating an alcohol extract of thymus with acetic acid. This possessed the same accelerating action on growth that has been repeatedly observed after feeding with whole thymus.

From a pancreas in which the ducts had been ligated for several weeks, and in which degeneration of the acini and hypertrophy of the islands of Langerhans had thus been produced, Banting and his fellow workers extracted with alcohol a substance, insulin, which, when injected into the blood, leads to a fall of blood sugar to the normal level, even in severe cases of diabetes.

CHAPTER XII

METHODS OF TESTING THE INTERNAL SECRETIONS

Hormones of endocrine glands can be obtained in a pure form only by methods competent to test their specific effects in minimal quantities. The methods which we possess at present may be divided into four groups; physiological methods—pursued by observing the effects produced on living animals; pharmacological methods—consisting of observations on surviving organs; serological methods; and operative methods. Physiological methods have already been considered here and there, but for the sake of a more complete survey they will be dealt with again at greater length.

The isolation and identification of pure adrenalin was effected by testing the action of different preparations on the blood pressure. In a rabbit narcotized with urethan, or a cat into which hirudin or a solution of peptone had been injected in order to prevent coagulation of the blood, one carotid was laid bare, its peripheral end was tied off, and it was connected at its central end by a canula and rubber tubing to a mercury manometer. A writing style was arranged to record the separate pulse waves on a kymograph; the movements of the style would thus show increased blood pressure by a rise in the height of the curve (see Fig. 13).

As a means of showing the specific action of the germ glands, I made use of the change in gas metabolism brought about by injections of germ gland extracts. Animals were enclosed in air-tight glass cylinders through which a current of air was passed by means of a water-vacuum pump. Before the air entered the respiration chamber it passed through tubes containing soda lime and concentrated sulphuric acid, by means of which all the carbon dioxide and water vapor were removed from the air. After its exit from the respiration chamber the air passed through two sets of U tubes, the first set of which contained pumice stone saturated with sulphuric acid, the second set, soda lime. By this means it was possible to determine by weight the water and carbon dioxide excreted during definite periods (Haldane's method).

Another process for studying germ gland hormones is Hermann's method of injecting preparations of a gland into virgin animals and taking the macroscopic and microscopic changes produced in the uterus and mammary glands as a measure of the activity of the preparation injected.

The action of the thyroid hormones has been investigated by feeding thyroid preparations to tadpoles, measuring their rate of growth and comparing the rate with that of their controls. The responsiveness of the vagus to electrical stimuli, as measured by the effect of vagus stimulation on blood pressure, has also been found to be a valuable method of testing the activity of the thyroid hormone. The relative strength of the induction currents

by which an identical rise in blood pressure is obtained before and after injection of a thyroid preparation furnishes a measure of its strength.

Tests which make use of surviving organs most frequently employ the Lawen-Trendelenburg frog preparation for determining vaso-motor effects. From a beheaded frog the alimentary canal is removed; the kidney blood vessels are ligated, and canules are placed in the abdominal aorta and the descending vena cava; the aortic canula is attached by rubber tubing to an elevated Mariotte's flask containing Ringer's solution with which the frog preparation can be so irrigated that a definite number of drops (usually 30 to 40 per minute) may trickle from the venous canula. The substance to be tested is injected into the rubber tubing which connects the arterial canula with the flask. A decrease or increase in the number of drops falling from the venous canula determines the vaso constrictor or vaso dilatator properties of the substance tested. The results may be recorded by a kymograph upon a revolving drum upon which the time is simultaneously registered.

To determine the action of hormones on the heart, Straub's method is frequently used. Into the right auricle of an isolated frog's heart, there is introduced a fine glass canula, distended at its free end and filled with Ringer's solution. The tip of the ventricle is attached by a fine thread to a writing lever, with which the heart's contractions are recorded by a kymograph. Instead of the whole heart, strips of heart muscle may also be used in this test.

A heart plethysmograph is constructed by inclosing the heart of an animal, in which artificial respiration is kept up, in a hemispherical glass bell closed by rubber sheeting. The variations of pressure produced in the enclosed air by the beating heart are transmitted to a writing lever and recorded on a drum.

The action of hypophysis preparations may be shown by suspending a guinea pig's uterus, or even a single horn of it in Ringer's solution at body temperature, and comparing its contractions with contractions produced by histamine solutions of known strength. Trendelenburg and Borgmann found that the extract of 1 gram of the posterior lobe had an action equal to about 0.17 grams of histamine. The influence of the hypophysis on smooth muscle tissue may likewise be shown by using strips of blood vessel, intestine or stomach.

Among serological methods use is made of Abderhalden's procedure for determining defense ferments; this, in case of disordered incretions, gives a method for detecting the presence of protective ferments circulating in the blood. In disorders of the endocrine glands, a portion of the suspected gland, plus the serum to be tested, is placed in a small dialyzing tube suspended in distilled water. The gland fragment must be previously boiled and washed until no ninhydrin reaction is obtained (blue color with triketohydrindenhydrate). If the serum contains ferments protective against the tested gland, the gland tissue used in the test will be broken down, its protein will be split into smaller dialyzable molecules, and within 16 to 24 hours the presence of these may be shown

in the outer fluid by boiling it with a ninhydrin solution of proper concentration.

Eiger showed the hormone action of thyroid on blood vessel preparations of the frog by means of the serum of rats that had been fed upon normal or hypertrophied thyroid glands. Such sera, added to subminimal doses of adrenalin, increased the constriction of frog's blood vessels.

CHAPTER XIII

THE INTERRELATIONSHIP OF THE ENDOCRINE GLANDS

We have so far spoken of the dominating influence of the internal secretions upon the physiological functions of the body; of the dependence of circulation, respiration, metabolism, body structure and instinct activity upon the endocrine hormones, some of which are still not even directly known.

It is important, also, to consider the endocrine organs from another viewpoint, that of their mutual relationships. It has been assumed that they constitute a closed ring, and that certain glands either promote or retard the action of others in the ring. From this conception arose the well-known schema according to which Falta, Eppinger, Rudinger and Hess represented the correlated action of a group of endocrine glands, a group which was afterwards enlarged by Aschner through the addition of the hypophysis and the ovary.

We have already discussed several examples of antagonistic and several of supplementary effects produced by the incretions of two different glands; adrenalin and hypophysin, we saw, have opposite actions on the kidney; the hypophysis and the thymus have coördinate effects in promoting skeletal growth. According to the schema which represents all the endocrine glands as one

interacting group, loss of the hypophyseal secretion, for instance, would cause increased ovarian secretion, and vice versa. But for only two glands has the work of recent years produced evidence of a mutually dependent relationship that is necessarily expressed by increased or diminished function, or by enlargement or reduction in the size of the two related glands. These are the hypophysis and the thyroid. However, the interaction which is now known to exist between this pair of glands was not represented in the schema to which reference has just been made.

If in dogs or rabbits the thyroid is removed, after a time a marked enlargement of the hypophysis occurs; the hypertrophy in this case affects only the anterior lobe, whereas the mid-lobe, judging from experiments made on cats, enlarges after all four of the parathyroids have also been removed. But if the thyroidectomized animals are fed thyroid gland substance the enlargement of the hypophysis does not take place. In congenital enlargement of the thyroid, there is, on the contrary, atrophy of the hypophysis (Livingston, Degener).

TABLE XV.

FIGURES ILLUSTRATING VICARIOUS ACTION OF THYROID AFTER HYPOPHYSIS REMOVAL

WEIGHT OF HYPOPHYSIS IN MG PRO KILO OF BODY WEIGHT					
ANIMALS FED WITH THYROID			ANIMALS NOT FED WITH THYROID		
	Control	Operated		Control	Operated
Male	12.81	13.26	Male	10.79	23.43
Female	14.56	14.72	Female	13.90	14.80

Feeding with the anterior hypophysis lobe causes the mortality from thyroidectomy to fall from 42.8 percent to 10.9 percent, a further proof of the vicarious action existing between these two glands (Larson).

Reciprocal action between the ovary and hypophysis, as indicated by Aschner's schema, is contradicted by recent findings. Removal of the ovaries from rabbits caused the hypophysis to increase in weight, from an average of 13 milligrams for each kilo of body weight to an average of 16.5 milligrams; but removal of the hypophysis, instead of the hypertrophy which should theoretically take place, results in a marked atrophy of the germ glands; and this diminished functional activity of the germ glands leads to the disease picture of dystrophia-adiposo-genitalis.

The basic evidence for the assumption that the hypophysis and the chromaffine system are mutually coöperative rests on the fact that the action of adrenalin is fortified after a previous injection of hypophysis extract. This heightened adrenalin action is due, according to Börner, to the slowing of the blood current, caused by the diminished force and size of the heart beat resulting from the preceding hypophyseal injection. By reason of this change in the velocity of the blood flow the adrenalin secreted in a definite time is distributed to a half or a third of the blood which normally contains it, and this increased concentration leads to a correspondingly increased action. This mechanical explanation of the coöperation between the two incretions is not contradictory to our previous assumption of an antagonism be-

tween the hypophysis and the suprarenal in regard to the causation of glycosuria; for in that case their opposition concerns only the functions of the kidney, and does not involve a mutual inhibition of their secretory functions.

We still need light on the question, whether there is coöperation between the thyroid and the germ glands. We saw, to be sure, that during pregnancy, with its change in ovarian function, the thyroid enlarged. But at this time, only one ovarian function, ovulation, is suppressed, whereas other functions that depend upon the activity of the interstitial tissue are augmented. Neither does lack of thyroid secretion lead to ovarian hypertrophy but, on the contrary, to atrophy with all its attendant disturbances.

Another assumed antagonism is one between the pancreas and the chromaffine system. Of this we have already adduced as examples the adrenal glycosuria after pancreas removal and the excessive dilatation of the pupil produced by instilling adrenalin into the eyes of animals from which the pancreas had been removed. The increased adrenalin action in the first instance, may be explained as due to the loss of the glycogen forming ferment ordinarily manufactured by the pancreas; in the absence of this ferment the liver fails to store up glucose which, therefore, enters the blood stream and causes glycosuria. A physiological antagonism between the pancreas and the chromaffine system seems also to be disproved by the fact that after pancreas removal adrenalin

causes no lasting mydriasis. The manifestations following pancreas removal may, therefore, be attributed to a general increase of irritability resulting from disordered metabolism; paralysis of the pupil sphincter caused by adrenalin would, for this reason, be more complete in pancreatomized than in normal animals (Joseph).

If the pancreas exerted a direct inhibitory action on the suprarenal, the secretion of adrenalin would be increased after the pancreas was removed. But dogs without a pancreas have no more adrenalin in the suprarenal gland than control dogs (Gley); nor is there evidence in microscopic preparations of greater activity in the suprarenal cells. The opposite method of studying this relationship by removal of the suprarenal gland cannot be made use of, because animals deprived of the suprarenals live but a short time after the operation.

The fact that diabetes mellitus disappears after removal of the thyroid has led to the view that there must be a physiological antagonism between it and the pancreas, and that this is indirectly manifested by way of the suprarenals, which after loss of the pancreas are led to increased production of adrenalin through stimulation by the thyroid. But it has never been possible to increase the production of adrenalin by injection of thyroid extract, and the explanation for the disappearance of glycosuria after thyroid removal lies most probably in the general lowering of metabolism, in the decreased absorption of carbohydrates from the intestines, in the diminished irritability of the sympathetic nervous sys-

tem, and in the dominant action of the hypophysis on kidney secretion—all due to the absence of the thyroid gland (see page 107).

All these examples are evidence of how little foundation there is for speaking of a fixed dependence of certain endocrine glands upon each other, and how little we are justified in assuming a rigid plan of action for the purpose of explaining the mutual relationships existing between the individual members of the endocrine gland system. The inhibiting or accelerating action exerted by a complex of incretions upon a physiological function will always depend upon the organ affected and the nature of its life processes. No schematic representation of the mutual interactions of the endocrine glands can do more than show their relations toward a single function. This we have endeavored to do by means of the foregoing examples (see pages 52, 107, 157, 158).

CHAPTER XIV

INTERNAL SECRETIONS AND THE NERVOUS SYSTEM

The constant and rapid spread of knowledge regarding the internal secretions creates the danger that the older teachings of Pflüger and Cuvier, according to which the life cycle is governed only by nerve impulses, may be replaced by extreme ideas of an opposite character; that there may arise a system of notions, according to which the incretions may be held to control all life processes, and the entire nervous system be regarded as subordinate to the endocrine glands. Should such a one-sided conception arise, it would be contradicted by the many definite facts already accumulated regarding the production of internal secretions through nerve stimulation. As familiar examples of the nervous excitation of incretory processes it may be mentioned that stimulation of the cervical sympathetic or of the thyroid nerves on one side causes an output of iodine from the thyroid on the stimulated side (Rahe, Watts), and that brain lesions are productive of anatomical and functional derangements in the thyroid, facts that have led Ceni to postulate special nerve centers for the thyroid and to locate them in the vertebrate forebrain, ascribing inhibitory, trophic, and vaso-motor characters to these centers.

Section of the suprarenal nerves causes atrophy of the

gland and a decrease in adrenalin production (Stewart), whereas an increased production of adrenalin may be induced by stimulation of the peripheral end of the sympathetic nerve lying within the thoracic cavity. It is also said that the production of adrenalin may be reflexly diminished by stimulation of the depressor nerve, even after adrenalin production had previously been artificially increased by stimulation of peripheral nerves (Richards and Woods).

Adrenalin production is also increased by exciting the sympathetic through alkaloids; small doses of nicotin and pilocarpin increase the adrenalin output. After the suprarenals have been removed or their veins ligated, alkaloids no longer cause pupil dilatation in cat's eyes that have been severed from the sympathetic ganglia (Cannon and Brieger).

Incretory activity can also be aroused by stimulation of special parts of the brain. The effect of puncture of the fourth ventricle on sugar metabolism has already been described; the same results may be obtained by electrical stimulation of the brain cortex. Elliot assumes the presence in the medulla, near the vaso-motor center, of a center regulating suprarenal activity, because of the fact that stimulation of the vaso-motor center leads to a markedly increased quantity of adrenalin in the blood, and to a decrease in the adrenalin content of the gland substance. Popielski believes that this diminished adrenalin content of the gland is caused by its greater irrigation with blood, resulting from vaso-motor dilatation; but evidence contradicting this explanation and pointing to

the existence of fibers influencing secretion is seen in the histological changes which are produced in the gland by stimulation of the splanchnic nerves, changes manifested by the disappearance of chromaffine granules.

That suprarenal functioning is influenced by psychical factors Cannon and de LePaz concluded from investigations that they made on cats that were intensely excited by a barking dog; the adrenalin content in the adrenal veins of these cats was said to be increased, this being shown by a heightened tonus of muscle strips exposed to the serum obtained from the excited animals. They also trace to adrenalin hyper-production many manifestations of sympathetic nerve stimulation, such as pupil dilatation, increase of blood pressure and pulse rate, inhibition of intestinal peristalsis, and related phenomena which occur in human beings during psychical excitement. Hopkins reached the same conclusion from his experiments dealing with psychical excitement, and with states of pain produced by irritation of peripheral nerves.

The pancreas incretion is also under nervous control. Stimulation of the vagus causes so rapid a fall of the blood sugar level that it seems justifiable to suppose that the hormone of the islands of Langerhans not only promotes glycogen production but accelerates the breaking down of sugar in the blood and tissues at the same time (deCorral).

The relations between the nervous system and the germ glands are still unexplained. Notwithstanding the convincing evidence obtained by transplantation experiments, and by injection of ovarian extracts into castrated

animals, investigations are still being undertaken in the hope of proving that the periodic phenomena of heat and menstruation are caused by cyclical stimuli coming from the nervous system, and that these stimuli cause ripening of the Graafian follicle and all the subsequent phenomena. The fundamental notion involved here is quite opposed to the Born-Fraenkel theory, that "the uterus is subject to cyclical trophic stimuli coming from the corpus luteum, an endocrine gland which undergoes periodic regeneration, the period being four weeks in the human being, and of varying lengths in other species."

The hypothesis which assumes a central nervous dominance of sexual manifestations is supported by the persistence of libido after castration and by the occurence of vicarious menstruation in the form of periodic hemorrhages from the nose or bowels, a phenomenon which persists for a long time in about 12 percent of the women whose ovaries have been removed. But if castration is performed before puberty, no libido and no menstruation occur, a sign that when these manifestations do occur in castrates they are initiated through an erotization of definite brain centers—an erotization that was produced by the incretions of the germ glands, and that began after the time of sexual maturity. The persistence of erotic manifestations after loss of the gonad incretion which normally excites the sexual impulse may, we have seen, be explained as due to "engrams" such as Semon imagines (page 225). Or these phenomena may be brought into the category of other nervous manifestations by assuming that their normally mediated operation

had created functional paths by way of which their recurrence is indirectly brought about after the direct stimulus is removed. But these theories lead to no explanation of the interdependence of brain and germ glands.

Equally difficult to answer is the question whether the incretion of the hypophysis reaches the brain cells directly, or only indirectly by way of the blood. Aschner believes in a visceral center in the floor of the third ventricle, a center from which sensory, sympathetic, and vagus fibers are given off, and of which electrical stimulation may cause contractions of the pregnant uterus, of the alimentary canal, and of the bladder. He assumes that the hypophyseal hormone reaches the third ventricle in conjunction with the lymph, by way of the mid-lobe, the posterior lobe, and the pituitary canal; and that the secretion acts there on the visceral center lying in the floor of the ventricle. But experiments on surviving organs show that the hypophyseal substance can stimulate the smooth muscle tissue of the uterus and of the blood vessels directly without the agency of such a center.

We should take warning from all these facts not to approach the problems of functional reciprocity with the purpose of showing that correlation is effected exclusively by either chemical or nervous processes. Both ways are possible. The nervous system controls the endocrine glands as well as the other body organs; on the other hand, the incretions have the power to influence both the peripheral end organs and the centers of the nervous system; and they may, by direct stimulation of the body cells, bring about the same functional changes, that nerve

stimuli produce. The secrets of life are not to be disclosed by the invention of doctrinaire formulations; their study demands rather that we take into account all the infinite multiplicity of the relationships between the different manifestations of life. The internal secretions are not an all-dominant force, but a force which shares the control of the life cycle with the brain and the autonomic nerve system.

The advances that have been brought about during the past thirty years verify the suspicion to which Brown-Sequard gave expression when he wrote in 1891: "It seems that the internal secretions are extremely useful in maintaining normal conditions in the living body; at times by exerting a directly favorable influence upon the organism; at times by preventing injurious actions from taking place within it."

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